Electronic Supplementary Information (ESI)

The role of indolyl substituents in squaramide-based anionophores

Giacomo Picci,[a] Israel Carreira-Barral,[b] Daniel Alonso-Carrillo,[b] Chiara Busonera,[a] Jessica Milia,[a] Roberto Quesada,[b*] and Claudia Caltagirone[a*]

[a]Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, S.S. 554 Bivio per Sestu, 09042 Monserrato (CA), Italy. [b]Departamento de Quimica, Facultad de Ciencias, Universidad de Burgos, 09001 Burgos, Spain

Contents

1. STRUCTURES OF THE STUDIED COMPOUNDS

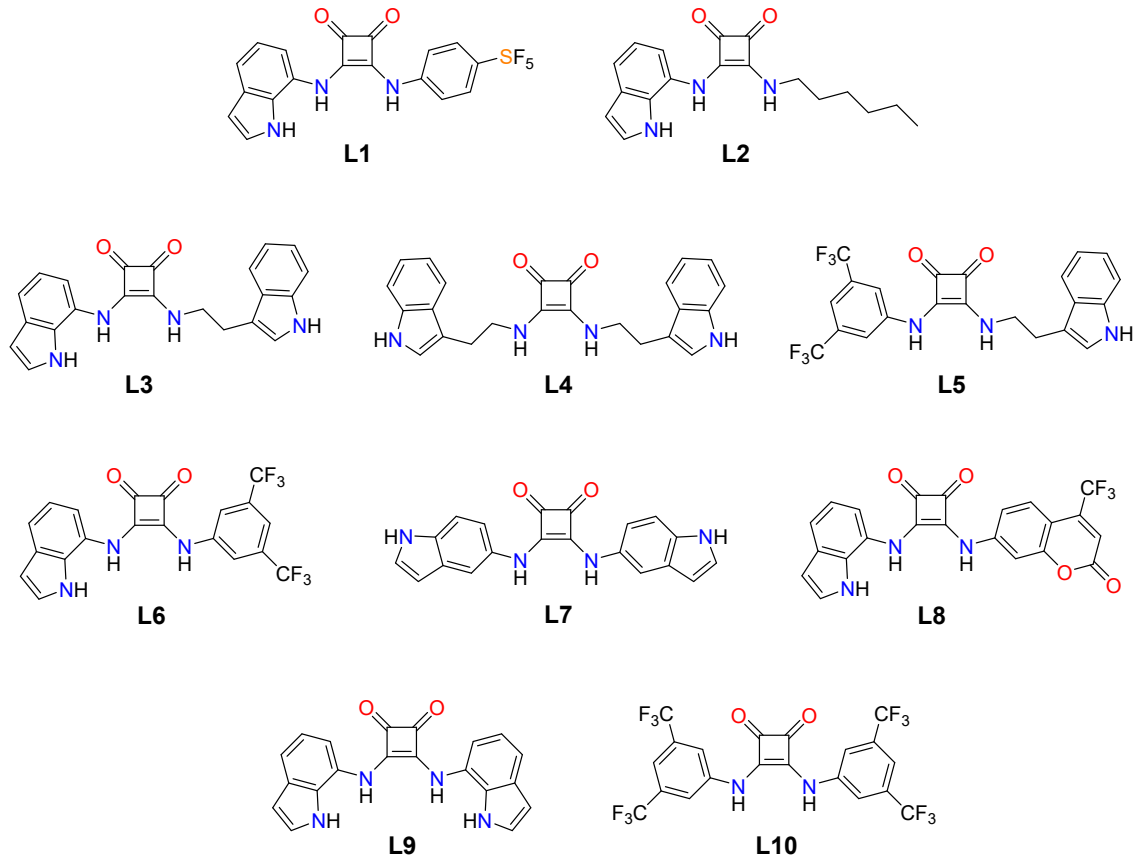


Chart 1. Structures of anionophores **L1**-**L8**, discussed in this work. **L9** and **L10** have been included in the study for comparative purposes.

2. SYNTHESES AND CHARACTERISATION DATA

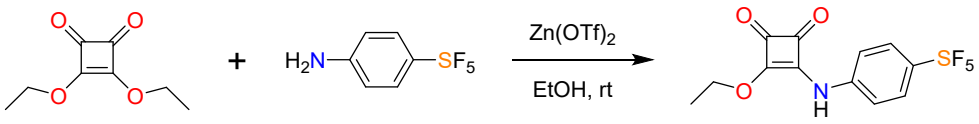
2.1. General procedures and methods

All reactions were performed in oven-dried glassware under a slight positive pressure of nitrogen. ^{1}H, ^{13}C and DEPT-135 NMR spectra were recorded on Bruker Avance 600 MHz (Nicholas Terrace, New York, NY, USA) or Varian Mercury 300 MHz spectrometers at 298 K. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm), calibrated to the residual solvent peak set, with coupling constants reported in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, s_b = broad singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line of a septet at δ = 39.52 ppm, for DMSO-d_6, or of a triplet at δ = 77.16 ppm, for $CDCl_3$. Elemental analyses were obtained using a PerkinElmer Series II – 2400 (Waltham, MA, USA). High-resolution mass spectra in positive ion mode were recorded on two spectrometers: (a) a triple quadrupole QqQ Varian 310-MS mass spectrometer using the atmospheric-pressure ESI technique (Lancashire, England). 20 µL of a DMSO solution of binder were introduced into the ESI source by a Varian HPLC pump without column, at a flow rate of 250 µL/min using a MeOH:H_2O 1:1 mixture. A dwell time of 4 s was used, together with needle voltage of 4000 V, shield voltage of 600 V, housing temperature of 60 °C, drying gas temperature of 400 °C, nebuliser gas pressure of 46 psi, drying gas pressure of 35 psi and a detector voltage of 1490 V. Mass spectra were acquired in the 250–500 amu range; (b) an Agilent 6545 Q-TOF mass spectrometer coupled to a 1260 Infinity liquid chromatographer from the same brand. All solvents and starting materials were purchased from commercial sources where available, and used as received without any further purification. Proton NMR titrations were performed by adding aliquots of the putative anionic guest (as the TBA salt, 0.075, 0.2 or 0.6 M), dissolved in a solution of the receptor (0.005 or 0.01 M) in DMSO-d_6/0.5% water, to a solution of the receptor (0.005 or 0.01 M).[1] X-ray diffraction analyses were performed on a Bruker D8 Venture diffractometer at 240 or 298 K.

[1] P. A. Gale, J. L. Sessler, V. Kral, V. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140-5141.

2.2. Intermediates

2.2.1. Intermediate 1



The procedure found in the literature was modified to prepare this compound.[2] A mixture of 3,4-diethoxycyclobut-3-en-1,2-dione (261 µL, 1.76 mmol), 4-pentafluorosulfanylaniline (338 mg, 1.54 mmol) and zinc(II) trifluoromethanesulfonate (10% mol) in ethanol (6 mL) was stirred at room temperature for 24 h. Reaction progress was monitored by TLC chromatography (SiO_2, 1:1 hexane:ethyl acetate). Once completed, the solvent was removed under reduced pressure and the crude was purified by column chromatography (SiO_2, 6:4 hexane:ethyl acetate). The fractions containing the desired product were combined and the solvent evaporated, giving a pale yellow solid. Yield: 380 mg, 1.11 mmol, 72%. ^{1}H NMR (300 MHz, DMSO-d_6, 298 K): δ (ppm) = 11.07 (s, 1H, NH), 7.90 (d, *J* = 9.1 Hz, 2H, ArH), 7.55 (d, *J* = 8.8 Hz, 2H, ArH), 4.79 (q, *J* = 7.1 Hz, 2H, CH), 1.43 (t, *J* = 7.1 Hz, 3H, CH). ^{13}C NMR {DEPT-135} (75 MHz, DMSO-d_6, 298 K): δ (ppm) = 187.3 (C), 184.5 (C), 179.4 (C), 169.5 (C), 147.7 (q_t, ^{2}J = 16.8 Hz, C), 141.4 (C), 127.1 (q_t, ^{3}J = 4.3 Hz, CH), 119.0 (CH), 70.1 (CH_2), 15.6 (CH_3). HR-MS (+ESI): found *m/z* = 344.0373 $[C_{12}H_{11}F_5NO_3S]^+$; calculated *m/z* = 344.0374.

[2] A. Rostami, A. Colin, X. Y. Li, M. G. Chudzinski, A. J. Lough and M. S. Taylor, *J. Org.Chem.*, 2010, **75**, 3983-3992.

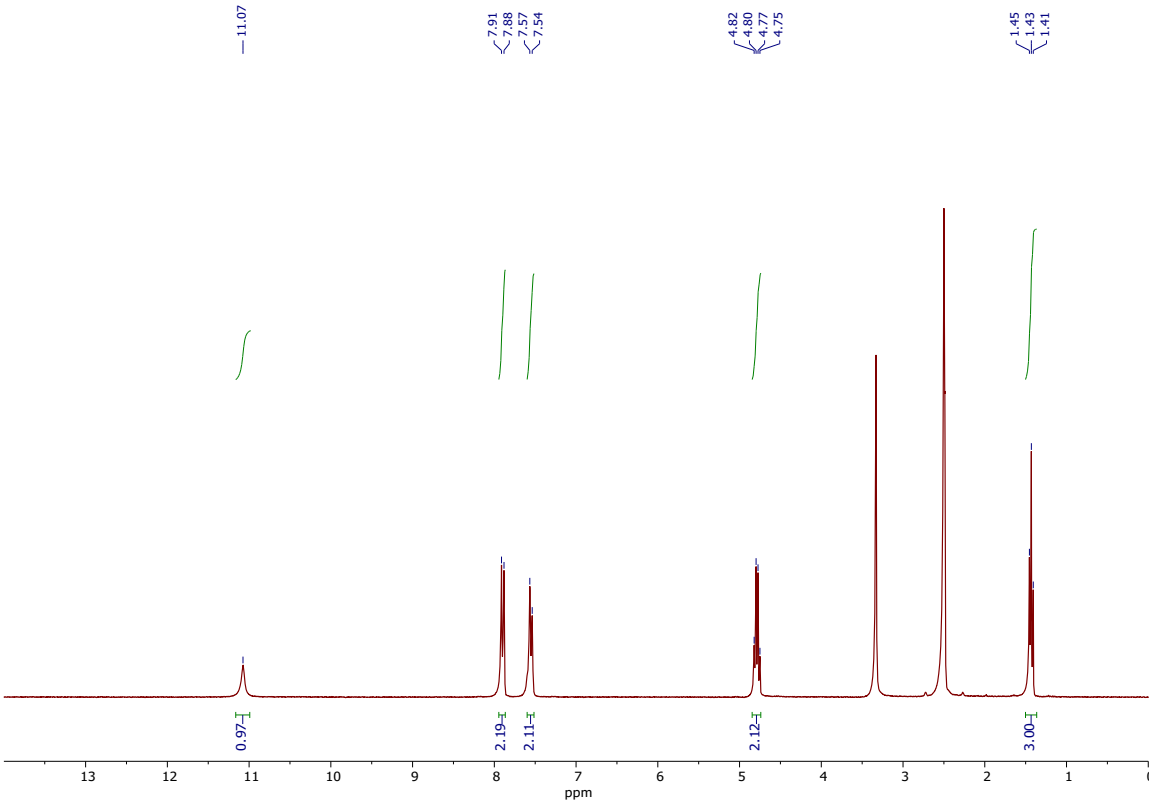


Figure S1. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, 298 K) for compound **Intermediate 1**.

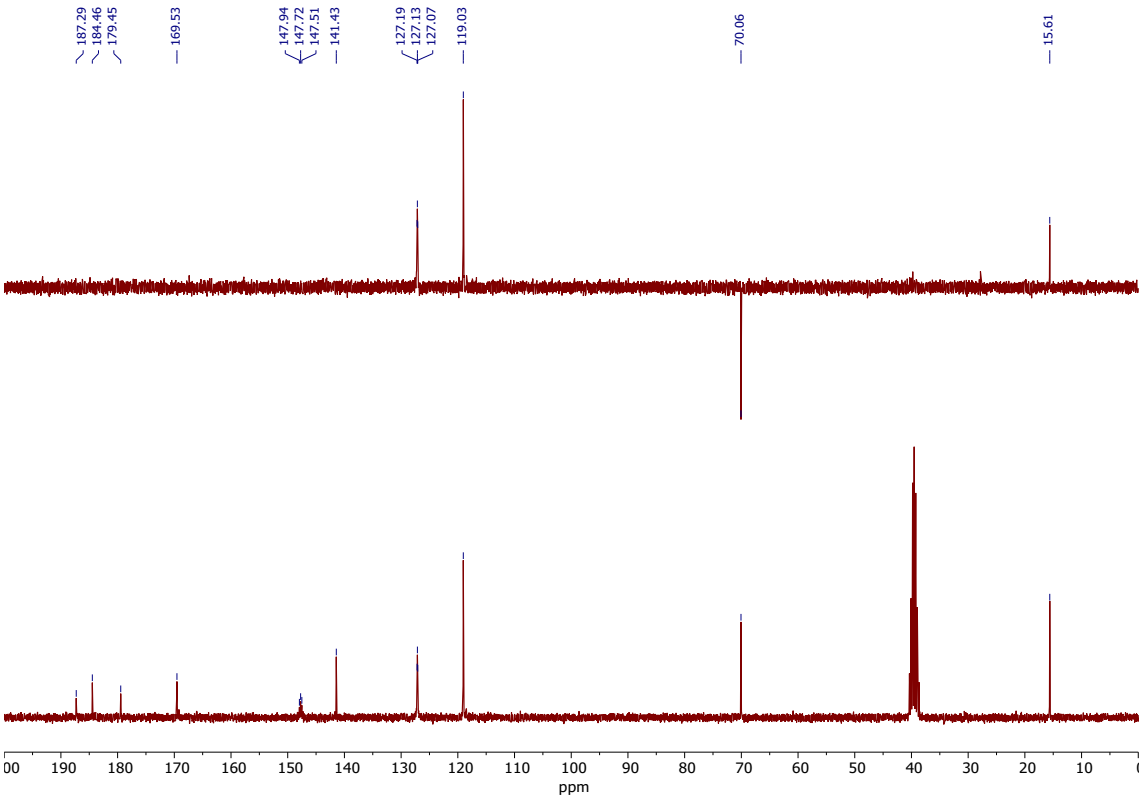


Figure S2. ^{13}C and DEPT-135 NMR spectra (75 MHz, DMSO-d_6, 298 K) for compound **Intermediate 1**.

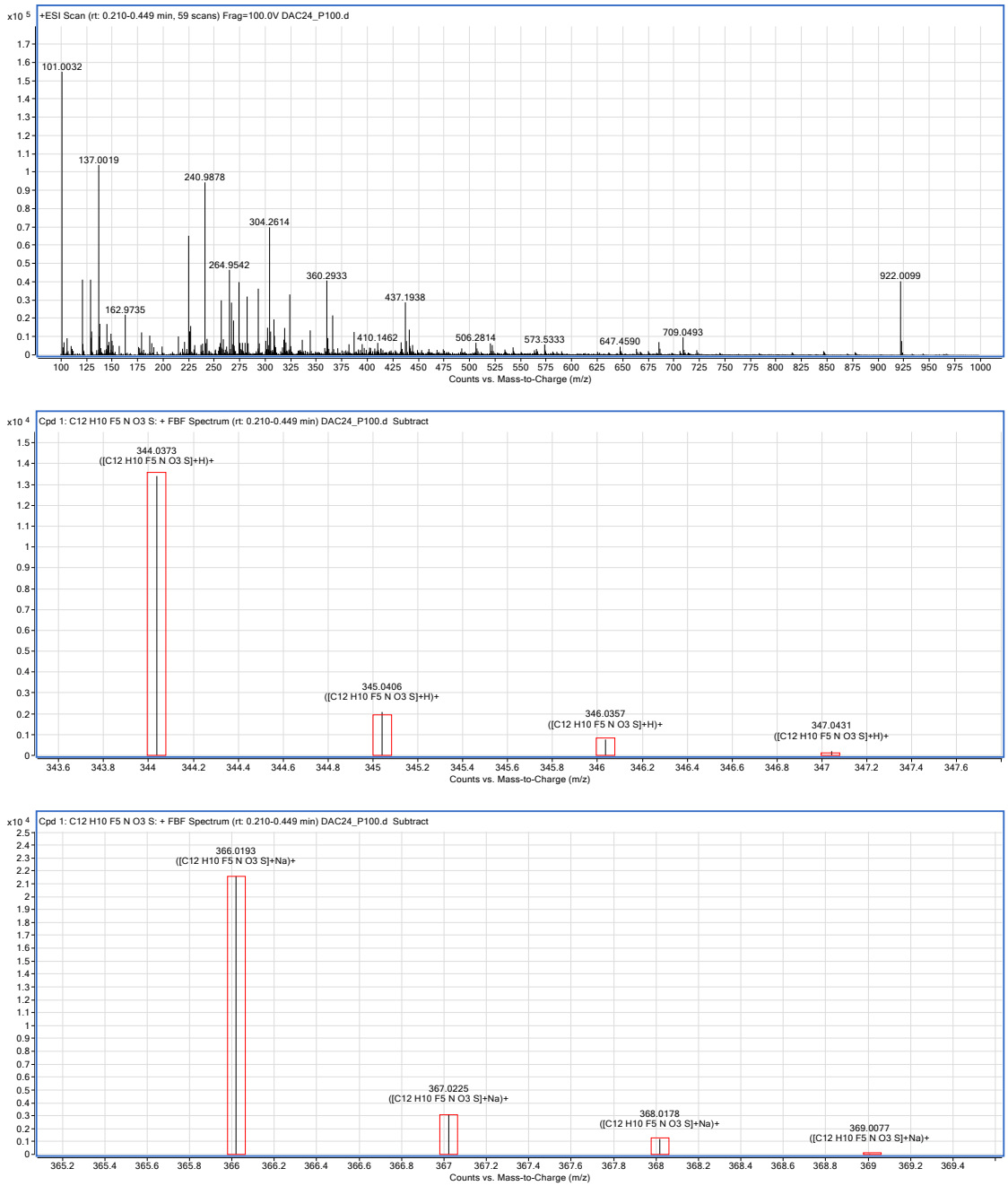
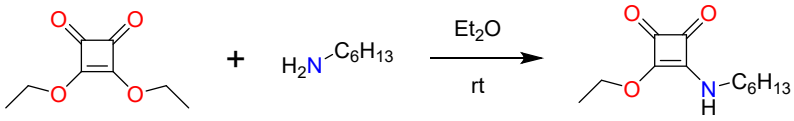


Figure S3. HR-MS (+ESI) spectrum for compound **Intermediate 1**.

2.2.2. Intermediate 2



The procedure found in the literature was modified to prepare this compound.[3] A mixture of 3,4-diethoxycyclobut-3-en-1,2-dione (174 µL, 1.17 mmol) and *n*-hexylamine (103 µL, 0.78 mmol) in diethyl ether (6 mL) was stirred at room temperature for 24 h. The resulting solution was concentrated to dryness under reduced pressure and the crude was purified by column chromatography (SiO_2, dichloromethane). The fractions containing the desired product were combined and the solvent removed, giving a white solid. Yield: 170 mg, 0.75 mmol, 97%. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.53 (t, *J* = 5.9 Hz, 0.75H, NH, rotamer A), 6.94 (t, *J* = 5.9 Hz, 0.25H, NH, rotamer B), 4.71-4.55 (m, 2H, CH), 3.54 (q, *J* = 6.4 Hz, 0.66H, CH, rotamer B), 3.34 (q, *J* = 6.8 Hz, 1.33H, CH, rotamer A), 1.63-1.09 (m, 12H, CH), 0.83-0.71 (m, 3H, CH). ^{13}C NMR {DEPT-135} (75 MHz, $CDCl_3$, 298 K): δ (ppm) = 189.6 (C, rotamer A), 189.2 (C, rotamer B), 182.9 (C, rotamer B), 182.3 (C, rotamer A), 177.0 (C, rotamer A), 176.8 (C, rotamer B), 172.9 (C, rotamer B), 172.4 (C, rotamer A), 69.4 (CH_2, rotamer A), 69.2 (CH_2, rotamer B), 44.7 (CH_2, rotamer A), 44.6 (CH_2, rotamer B), 31.1 (CH_2, rotamer A), 30.8 (CH_2, rotamer B), 30.3 (CH_2, rotamer A), 29.5 (CH_2, rotamer B), 25.8 (CH_2, rotamer A), 22.3 (CH_2, rotamer A), 15.7 (CH_3, rotamer A), 15.6 (CH_3, rotamer B), 13.8 (CH_3, rotamer A). HR-MS (+ESI): found *m/z* = 226.1439 $[C_{12}H_{20}NO_3]^+$; calculated *m/z* = 226.1438.

[3] M. C. Rotger, M. N. Piña, A. Frontera, G. Martorell, P. Ballester, P. M. Deyà and A. Costa, *J. Org. Chem.*, 2004, **69**, 2302-2308.

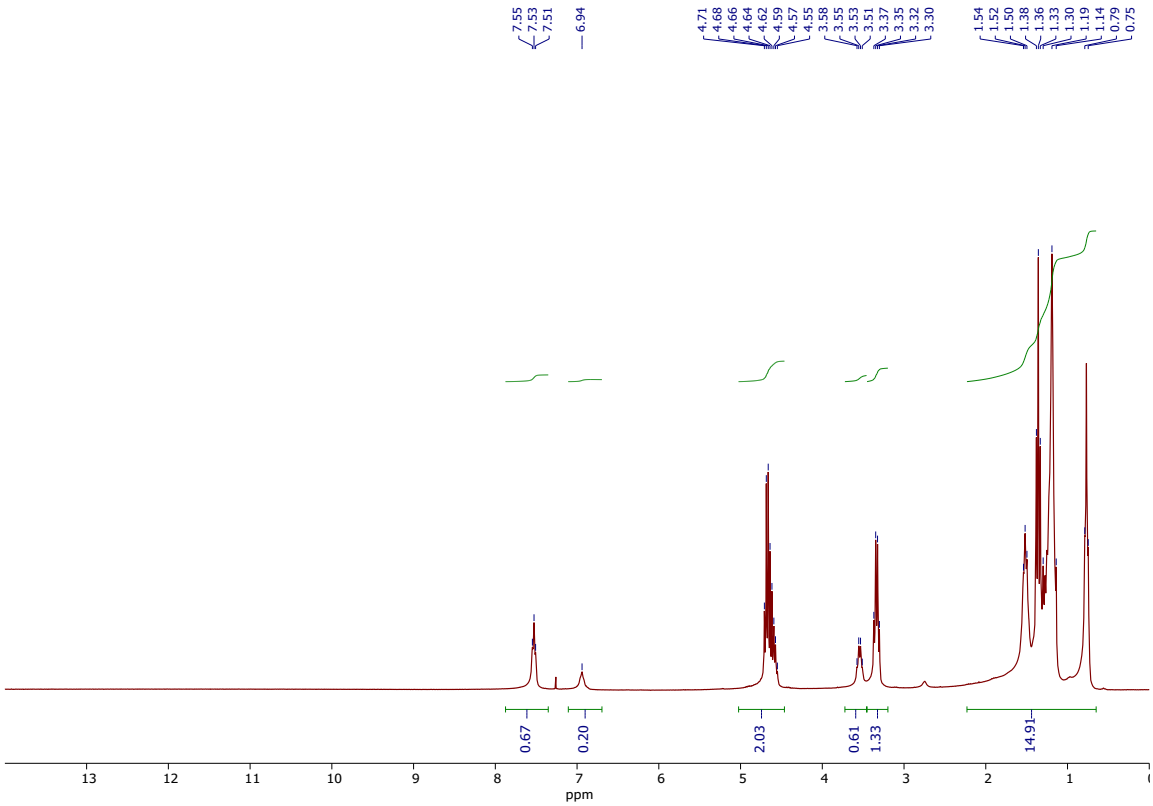


Figure S4. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, 298 K) for compound **Intermediate 2**.

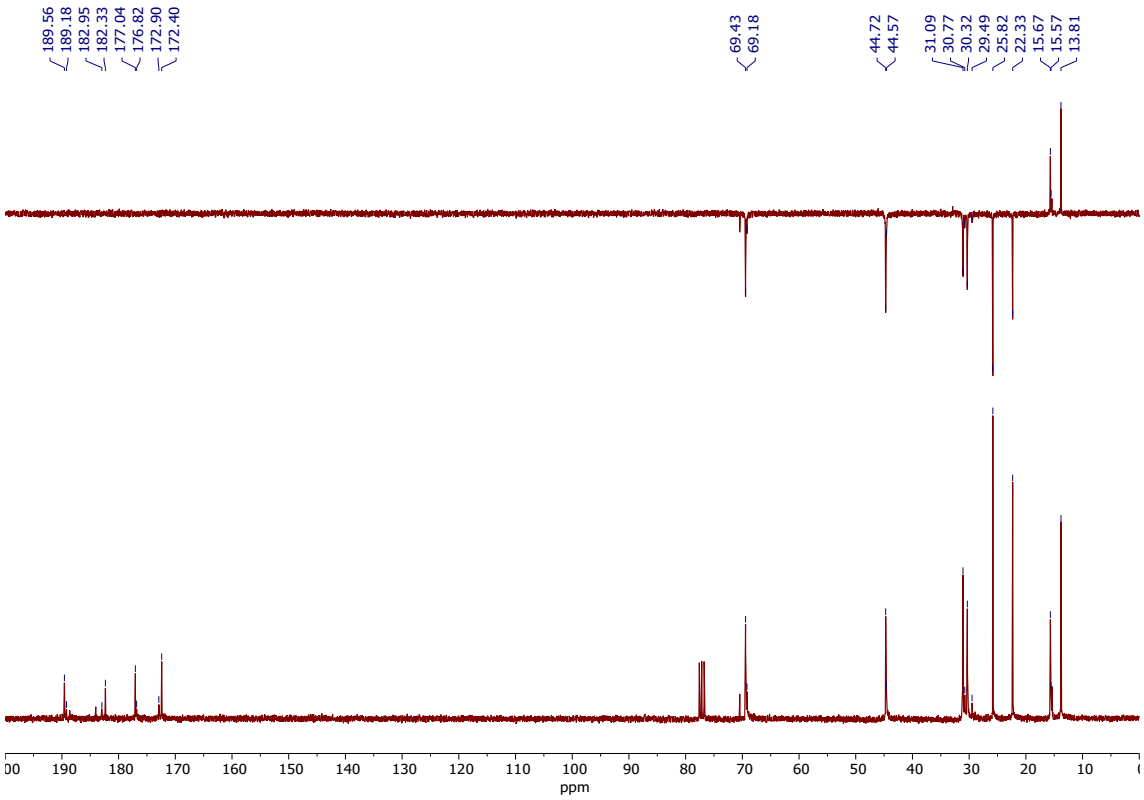


Figure S5. ^{13}C and DEPT-135 NMR spectra (75 MHz, $CDCl_3$, 298 K) for compound **Intermediate 2**.

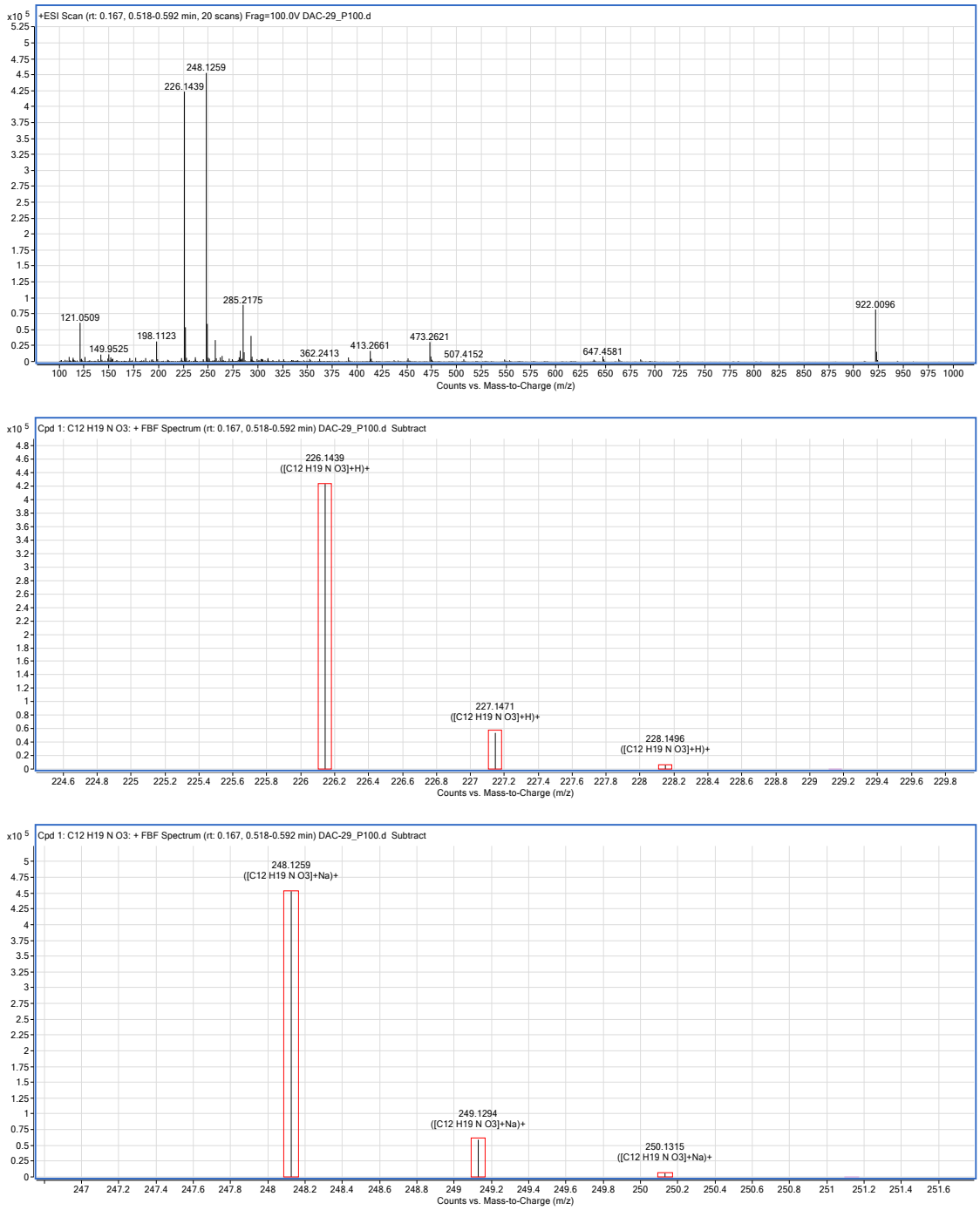
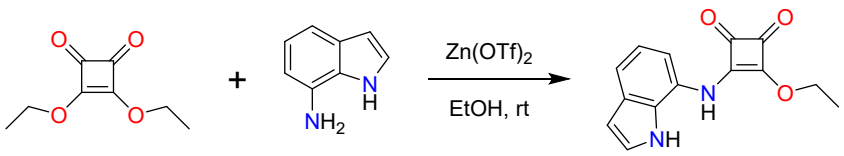


Figure S6. HR-MS (+ESI) spectrum for compound **Intermediate 2**.

2.2.3. Intermediate 3



The procedure found in the literature was modified to prepare this compound.[2] To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (200 mg, 1.18 mmol) and zinc(II) trifluoromethanesulfonate (10% mol) in dry ethanol (10 mL) at room temperature, 7-aminoindole (140 mg, 1.06 mmol) was added. Reaction progress was monitored by TLC chromatography (SiO_2, 1:1 hexane:ethyl acetate). Once completed, the solvent was removed under reduced pressure and the crude was purified by column chromatography (SiO_2, 3:2 hexane:ethyl acetate). The fractions containing the desired product were combined and the solvent evaporated, collecting it as crude brown solid. Yield: 250 mg, 0.97 mmol, 92%. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ (ppm): 11.07 (s, 1H, NH), 10.58 (s, 1H, NH), 7.47 (d, *J* = 7.7 Hz, 1H, ArH), 7.44 (t, *J* = 2.3 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.05 (t, *J* = 7.7 Hz, 1H, ArH), 6.55 (t, *J* = 2.1 Hz, 1H, ArH), 4.74 (q, *J* = 7.1 Hz, 2H, CH), 1.39 (t, *J* = 7.3 Hz, 3H, CH). ^{13}C NMR (151 MHz, DMSO-d_6, 298 K) δ (ppm): 184.6, 178.7, 171.0, 129.8, 129.4, 126.2, 122.7, 119.4, 118.2, 114.9, 102.2, 69.7, 16.0. Elemental analysis: % calc. for $C_{14}H_{12}N_2O_3$ (% found): C: 65.62 (65.21); H: 4.72 (4.79); N: 10.93 (10.87); O: 18.73 (19.13).

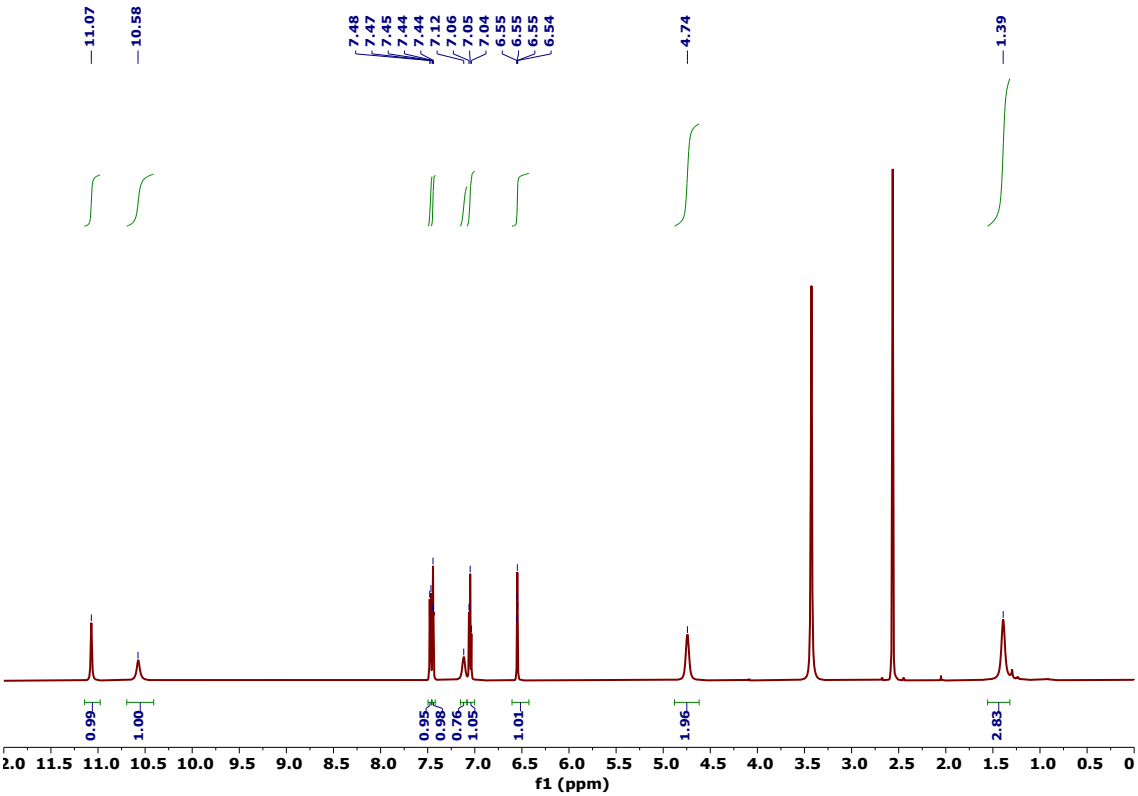


Figure S7. ^{1}H NMR spectrum (600 MHz, DMSO-d_6, 298 K) for compound **Intermediate 3**.

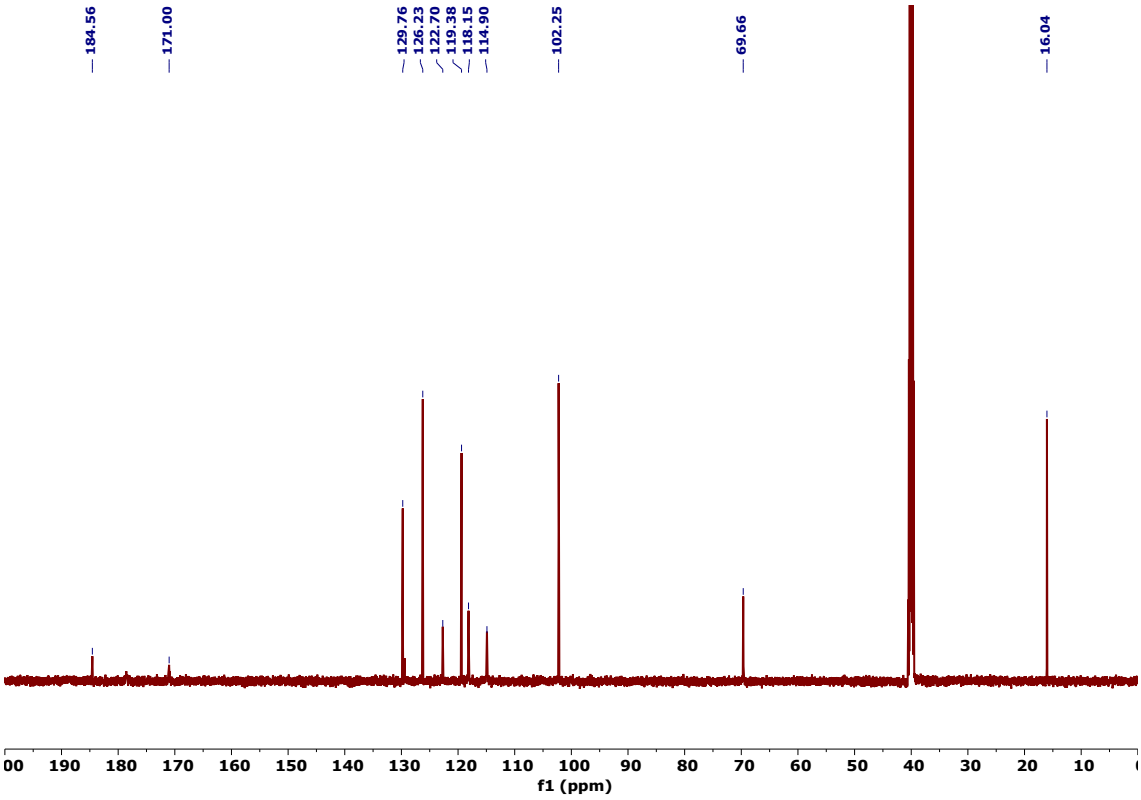
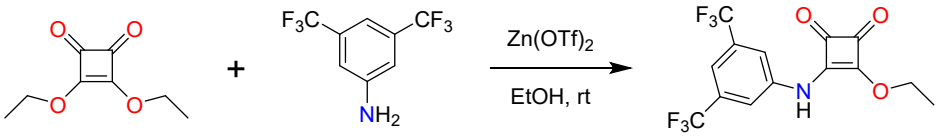


Figure S8. ^{13}C NMR spectrum (151 MHz, DMSO-d_6, 298 K) for compound **Intermediate 3**.

2.2.4. Intermediate 4



The procedure found in the literature was modified to prepare this compound.[2] To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (200 mg, 1.18 mmol) and zinc(II) trifluoromethanesulfonate (10% mol) in dry ethanol (10 mL) at room temperature, 3,5-bis(trifluoromethyl)aniline (240 mg, 1.06 mmol) was added. Reaction progress was monitored by TLC chromatography (SiO_2, 1:1 hexane:ethyl acetate). Once completed, the solvent was removed under reduced pressure and the crude was purified by column chromatography (SiO_2, from 1:1 hexane:ethyl acetate to 1:2 hexane:ethyl acetate). The fractions containing the desired product were combined and the solvent evaporated, collecting it as crude pale green solid. Yield: 310 mg, 0.87 mmol, 84%. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ (ppm): 11.20 (s, 1H, NH), 8.04 (s, 2H, ArH), 7.78 (s, 1H, ArH), 4.80 (q, J = 7.1 Hz, 2H, CH), 1.42 (t, J = 7.3 Hz, 3H, CH). ^{13}C NMR (151 MHz, DMSO-d_6, 298 K) δ (ppm): 187.9 , 185.0, 179.7, 169.6, 140.6, 131.6 (q, ^{2}J = 33 Hz, CF_3), 123.6 (q, ^{1}J = 270 Hz, CF_3), 119.9, 116.8, 70.6, 15.8. Elemental analysis: % calc. for $C_{14}H_9F_6NO_3$ (% found): C: 47.61 (47.41); H: 2.57 (2.51); F: 32.27 (32.47); N: 3.97 (3.87); O: 13.59 (13.64).

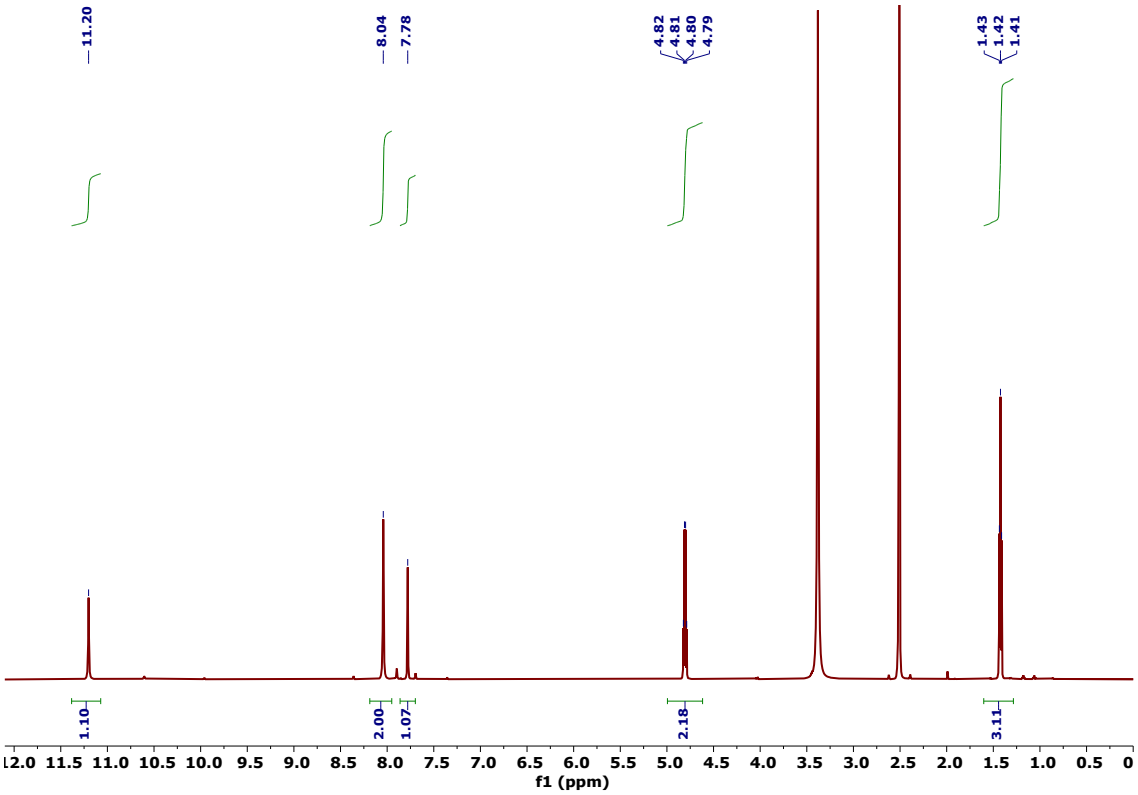


Figure S9. ^{1}H NMR spectrum (600 MHz, DMSO-d_6, 298 K) for compound **Intermediate 4**.

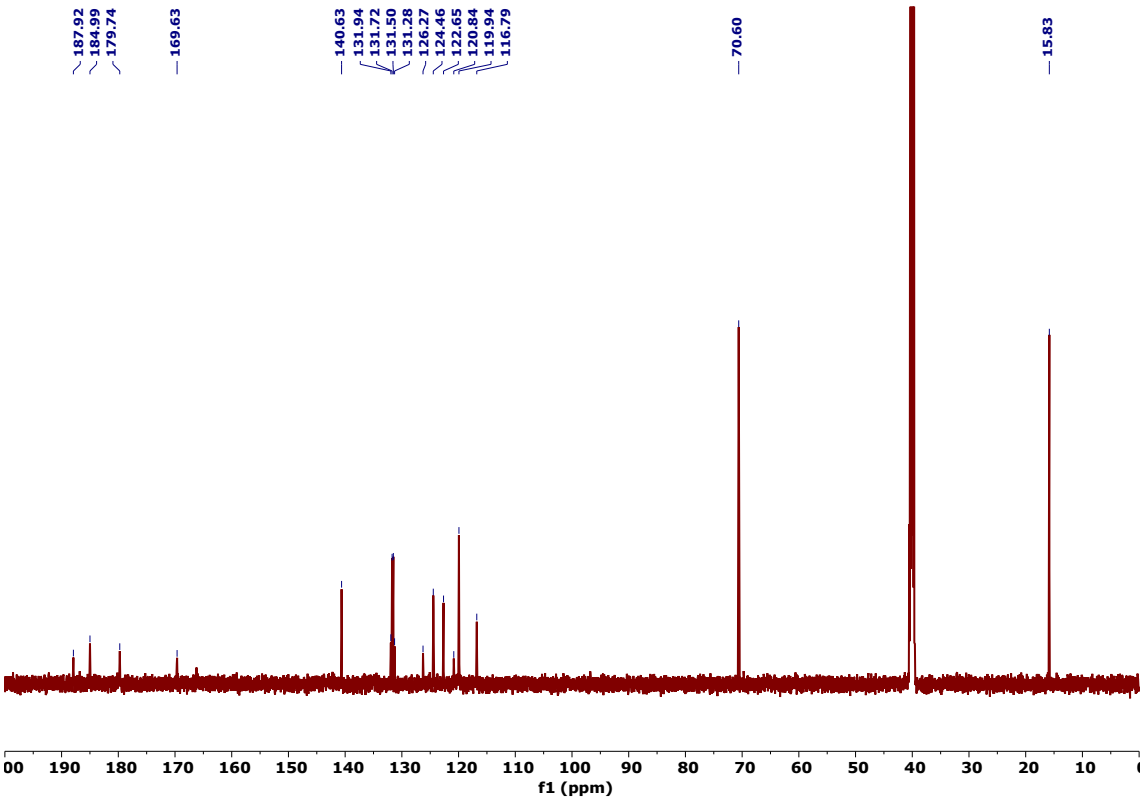
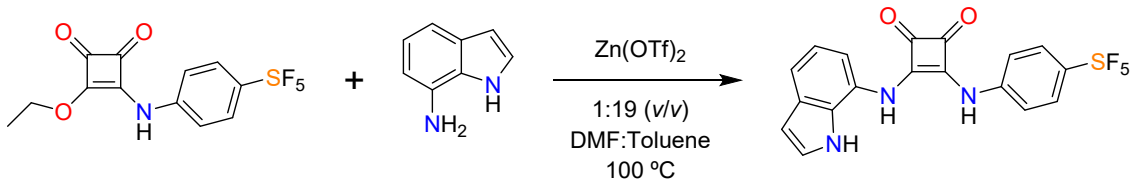


Figure S10. ^{13}C NMR spectrum (151 MHz, DMSO-d_6, 298 K) for compound **Intermediate 4**.

2.3. Squaramides

2.3.1. L1



The procedure found in the literature was modified to prepare this compound.[2] A mixture of **intermediate 1** (205 mg, 0.60 mmol), 7-aminoindole (77 mg, 0.58 mmol) and zinc(II) trifluoromethanesulfonate (20% mol) in a 1:19 (*v*/*v*) dimethylformamide:toluene mixture (1 mL) was heated at 100 °C for 72 h. Upon cooling to room temperature, methanol (10 mL) was added and the solution was kept in the freezer for 24 h. The resulting brown solid was isolated by filtration, washed with cold methanol (3 × 5 mL) and diethyl ether (3 × 5 mL), and dried under vacuum. Yield: 170 mg, 0.39 mmol, 68%. ^{1}H NMR (300 MHz, DMSO-d_6, 298 K): δ (ppm) = 11.11 (s, 1H, NH), 10.18 (s, 1H, NH), 9.86 (s, 1H, NH), 7.85 (d, *J* = 8.6 Hz, 2H, ArH), 7.56 (d, *J* = 8.6 Hz, 2H, ArH), 7.43-7.38 (m, 2H, ArH), 7.03-6.95 (m, 2H, ArH), 6.52-6.48 (m, 1H, ArH). ^{13}C NMR {DEPT-135} (75 MHz, DMSO-d_6, 298 K): δ (ppm) = 184.0 (C), 182.9 (C), 168.5 (C), 165.1 (C), 147.6 (q, ^{2}J = 17 Hz, C), 142.4 (C), 129.9 (C), 129.7 (C), 127.7 (q, ^{3}J = 3.9 Hz, CH), 126.5 (CH), 122.7 (C), 119.7 (CH), 118.7 (CH), 118.5 (CH), 115.5 (CH), 102.7 (CH). HR-MS (+ESI): found *m/z* = 430.0641 $[C_{18}H_{13}F_5N_3O_2S]^+$; calculated *m/z* = 430.0643.

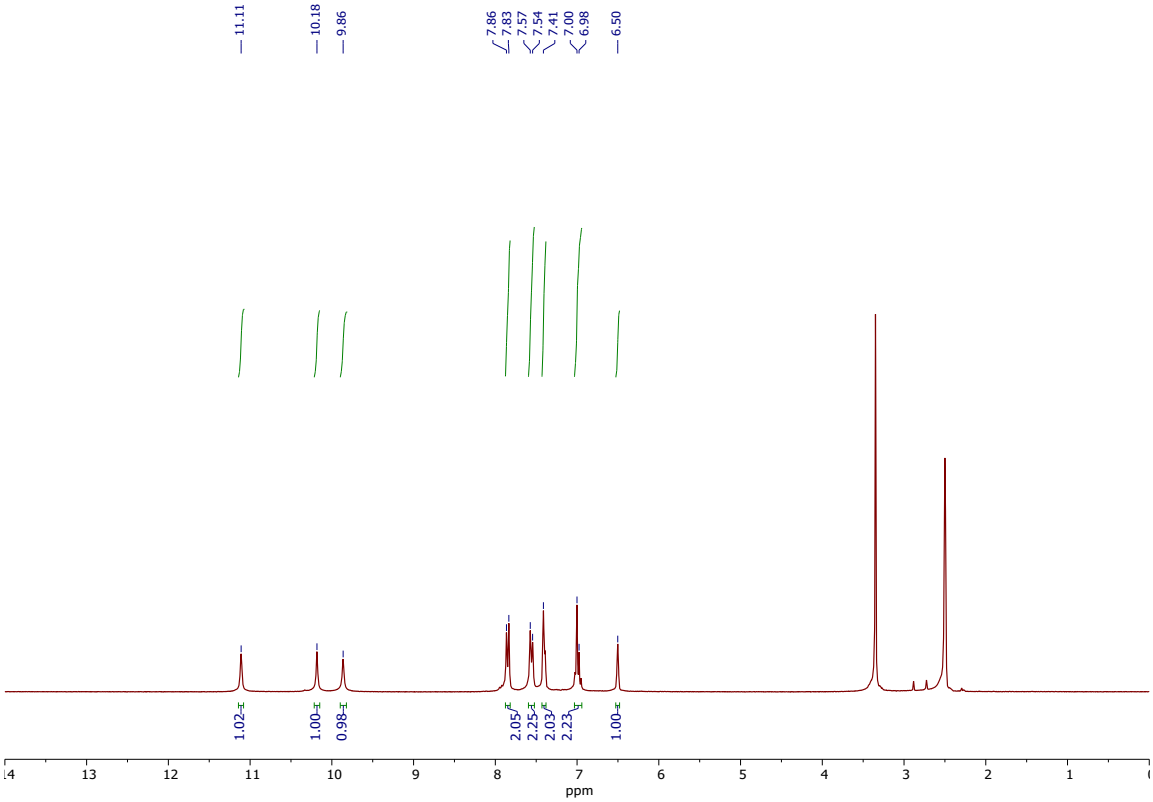


Figure S11. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, 298 K) for compound **L1**.

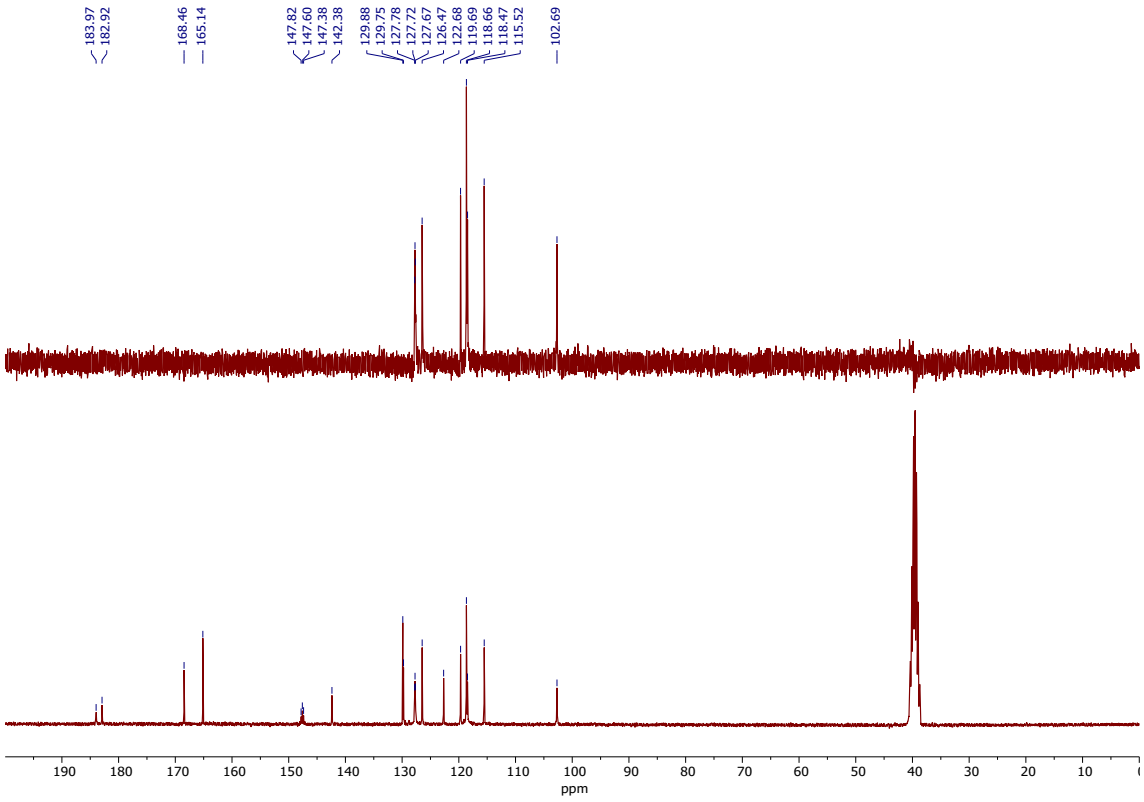


Figure S12. ^{13}C and DEPT-135 NMR spectra (75 MHz, DMSO-d_6, 298 K) for compound **L1**.

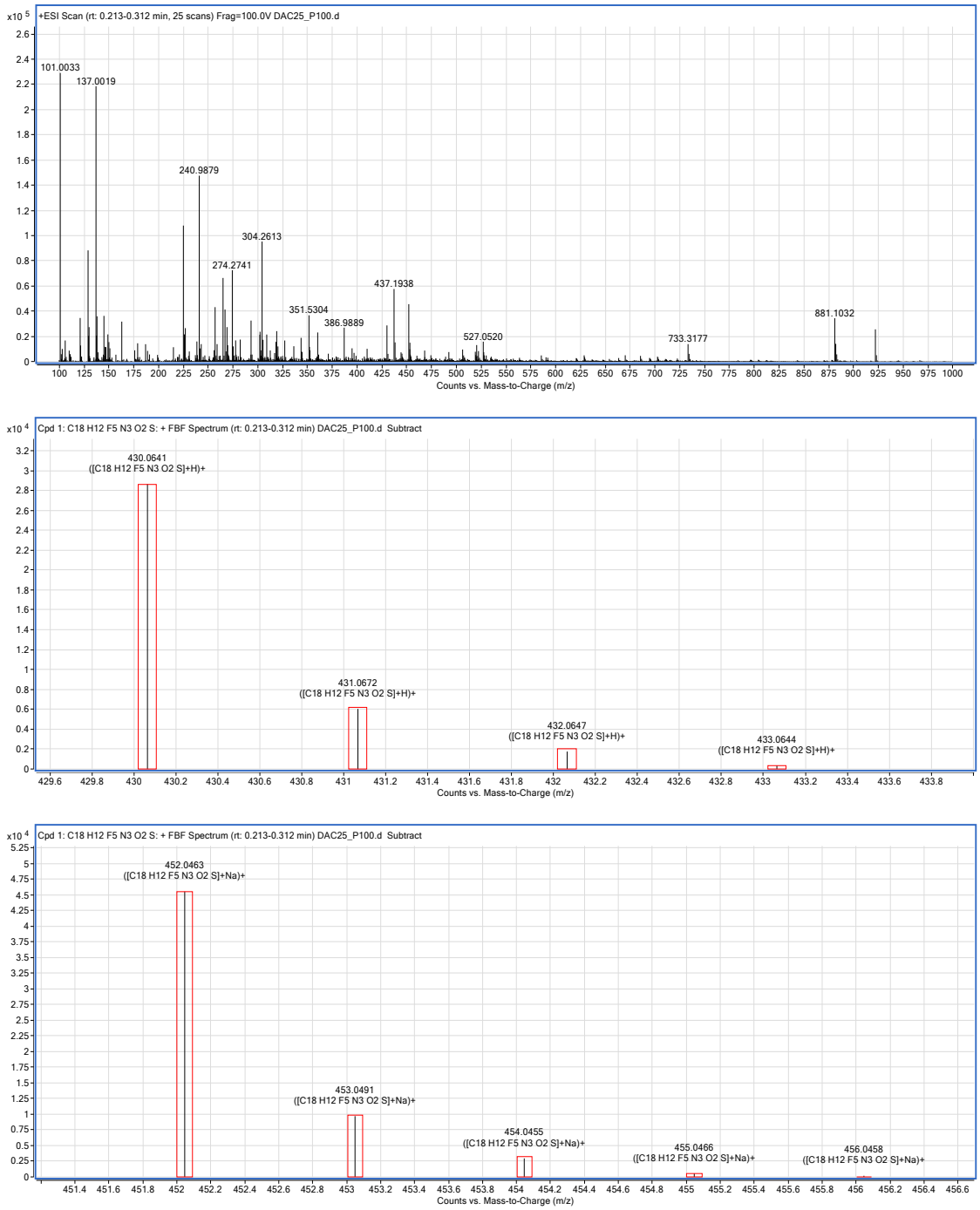
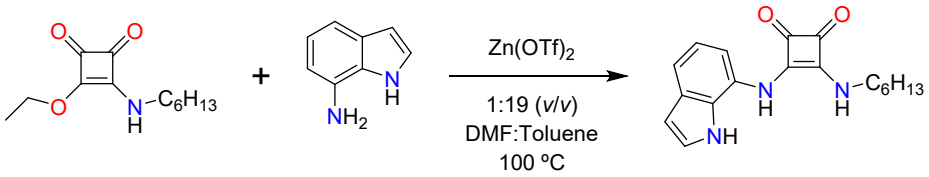


Figure S13. HR-MS (+ESI) spectrum for compound **L1**.

2.3.2. L2



The procedure found in the literature was modified to prepare this compound.[2] A mixture of **intermediate 2** (170 mg, 0.75 mmol), 7-aminoindole (82 mg, 0.62 mmol) and zinc(II) trifluoromethanesulfonate (20% mol) in a 1:19 (*v*/*v*) dimethylformamide:toluene mixture (1 mL) was heated at 100 °C for 24 h. Upon cooling to room temperature, methanol (10 mL) was added and the solution kept in the freezer for 24 h. The resulting brown solid was isolated by filtration, washed with cold methanol (3 × 5 mL) and diethyl ether (3 × 5 mL), and dried under vacuum. Yield: 120 mg, 0.38 mmol, 62%. ^{1}H NMR (300 MHz, DMSO-d_6, 298 K): δ (ppm) = 10.94 (s, 1H, NH), 9.52 (s, 1H, NH), 7.45-7.28 (m, 3H, ArH), 7.04-6.91 (m, 2H, ArH), 6.51-6.46 (m, 1H, NH), 3.59 (s_b, 2H, CH), 1.69-1.11 (m, 8H, CH), 0.94-0.79 (m, 3H, CH). ^{13}C NMR {DEPT-135} (75 MHz, DMSO-d_6, 298 K): δ (ppm) = 184.7 (C), 181.1 (C), 169.2 (C), 164.5 (C), 129.2 (C), 128.5 (C), 125.7 (CH), 123.1 (C), 119.3 (CH), 116.6 (C), 113.4 (C), 102.0 (CH), 43.7 (CH_2), 30.9 (CH_2), 30.7 (CH_2), 25.6 (CH_2), 22.1 (CH_2), 13.9 (CH_3). HR-MS (+ESI): found *m/z* = 312.1707 $[C_{18}H_{22}N_3O_2]^+$; calculated *m/z* = 312.1707.

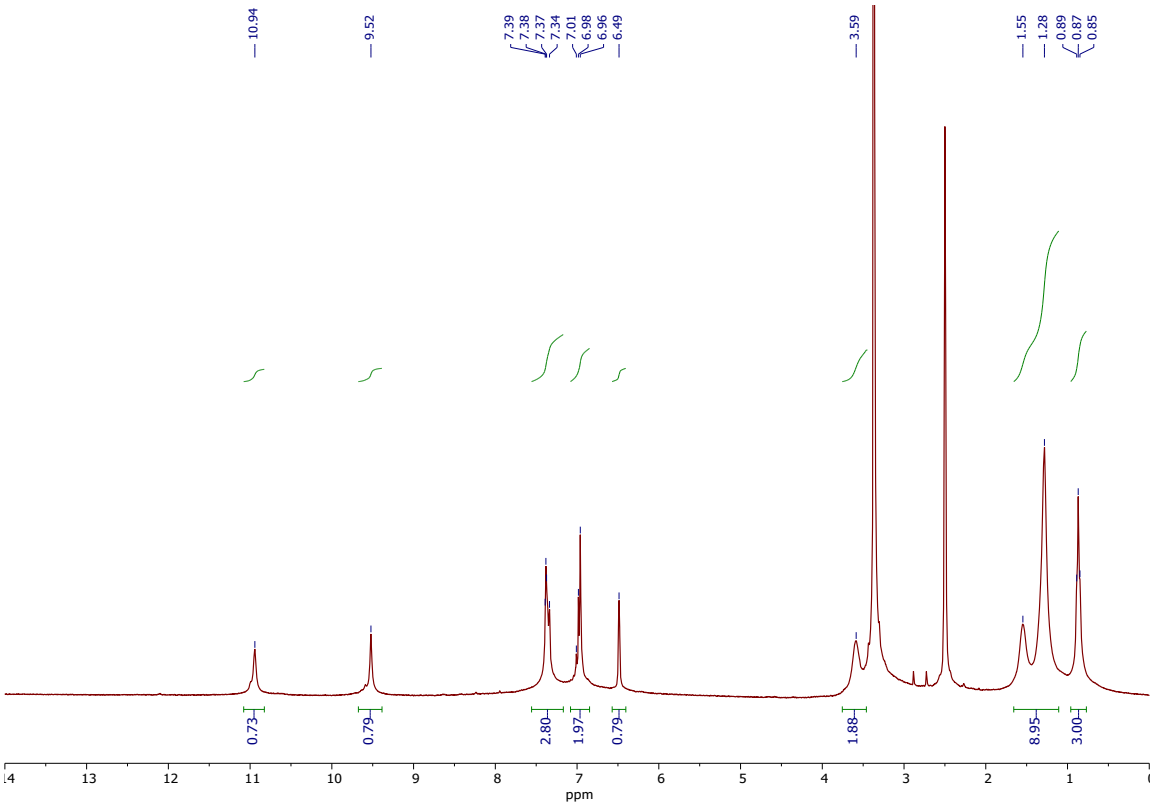


Figure S14. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, 298 K) for compound **L2**.

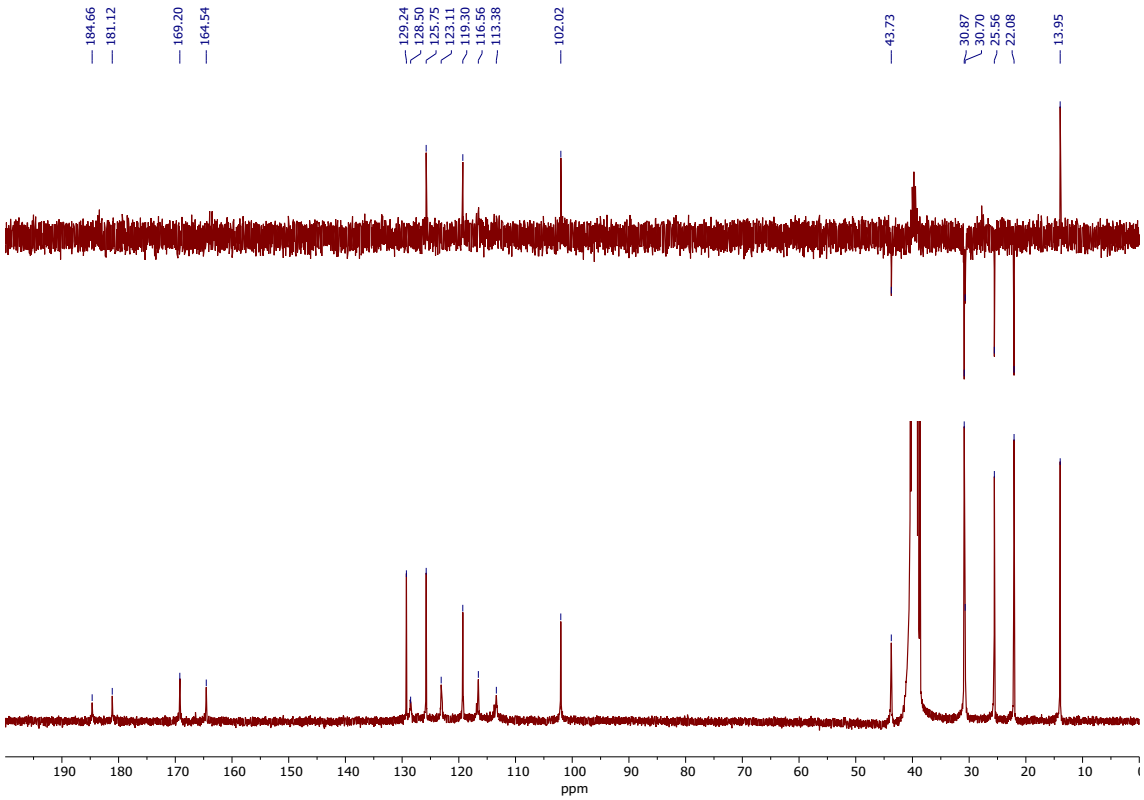


Figure S15. ^{13}C and DEPT-135 NMR spectra (75 MHz, DMSO-d_6, 298 K) for compound **L2**.

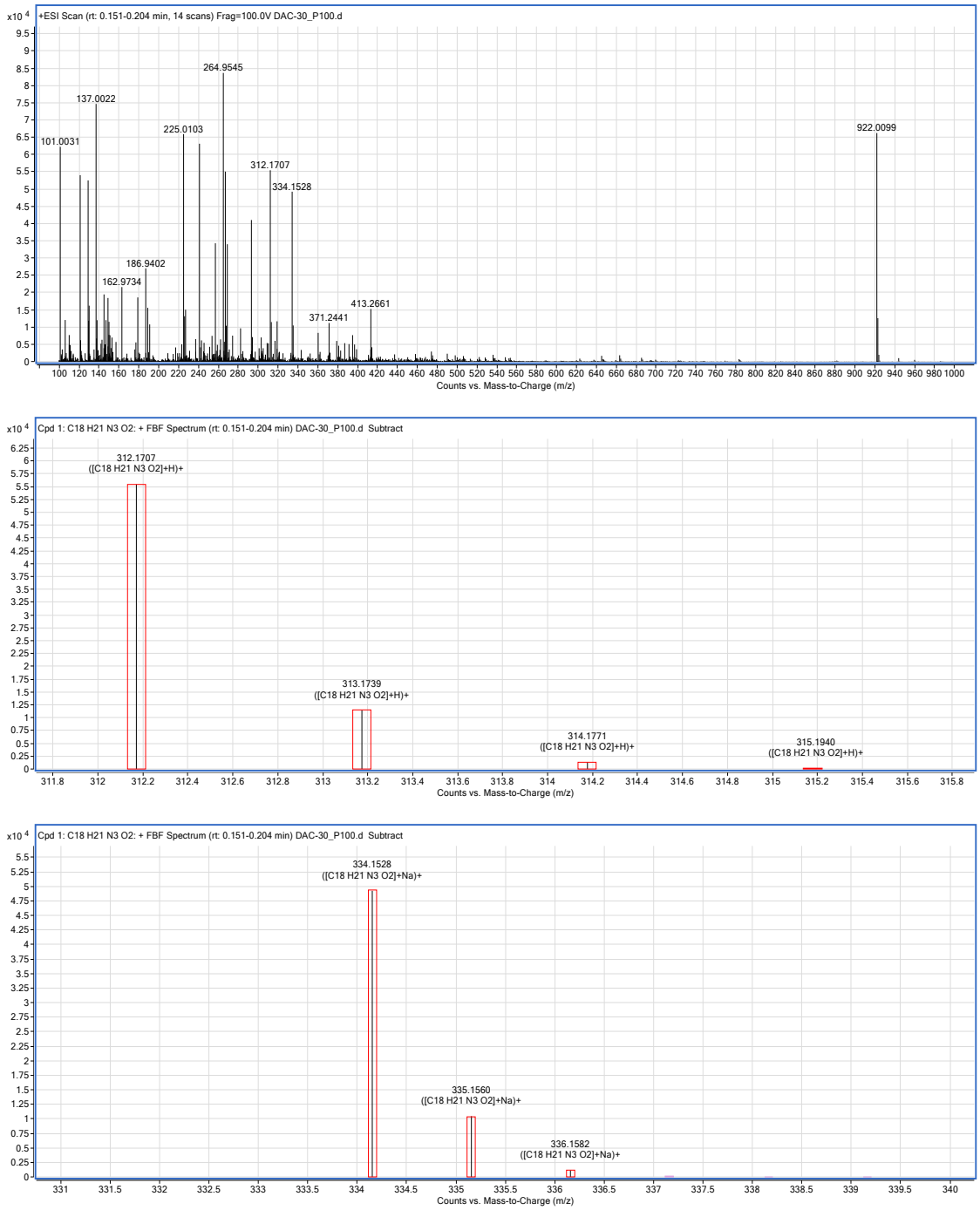
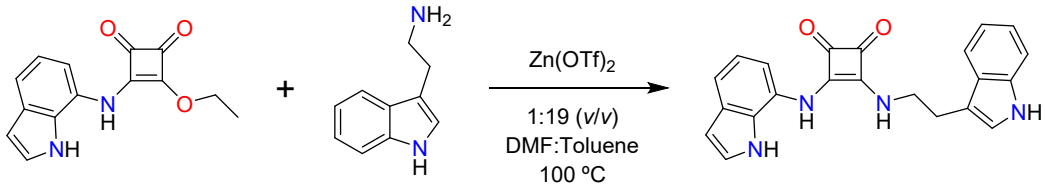


Figure S16. HR-MS (+ESI) spectrum for compound **L2**.

2.3.3. L3



The procedure found in the literature was modified to prepare this compound.[2] To a stirred solution of **intermediate 3** (150 mg, 0.59 mmol) and zinc(II) trifluoromethanesulfonate (20% mol) in a 1:19 (*v*/*v*) dimethylformamide:toluene mixture (5 mL) at 100 °C, 3,5-bis(trifluoromethyl)aniline (148 mg, 0.64 mmol) was added. Reaction progress was monitored by TLC chromatography (SiO_2, 1:1 hexane:ethyl acetate). Once completed, the solvent was removed under reduced pressure. The crude oil was taken up with ethyl acetate and precipitated with hexane. The precipitate was filtered and dried under vacuum; the product was collected as a dark green solid. Yield: 140 mg, 0.38 mmol, 65%. M. p. > 165 °C. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ (ppm): 10.88 (s, 2H, NH), 9.56 (s, 1H, NH), 7.63 (s, 1H, NH), 7.41-7.29 (m, 4H, ArH), 7.21 (s, 1H, ArH), 7.08 (t, *J* = 7.2 Hz, 1H, ArH), 6.99 (t, *J* = 6.6 Hz, 1H, ArH), 6.94 (t, *J* = 7.2 Hz, 1H, ArH), 6.89 (d, *J* = 6.4 Hz, 1H, ArH), 6.48 (s, 1H, ArH), 3.92 (s, 2H, CH), 3.02 (s, 2H, CH). ^{13}C NMR (151 MHz, DMSO-d_6, 298 K) δ (ppm): 181.8, 165.1, 136.8, 129.7, 127.6, 126.2, 123.5, 121.5, 119.8, 118.9, 118.2, 117.0, 111.9, 111.2, 102.5, 44.7, 27.6. Elemental analysis: % calc. for $C_{22}H_{18}N_4O_2$ (% found): C: 71.34 (71.22); H: 4.90 (4.98); N: 15.13 (15.25); O: 8.64 (8.51). HR-MS (+ESI): found *m/z* = 370.1435 [$C_{22}H_{18}N_4O_2$]; calculated *m/z* = 370.1430.

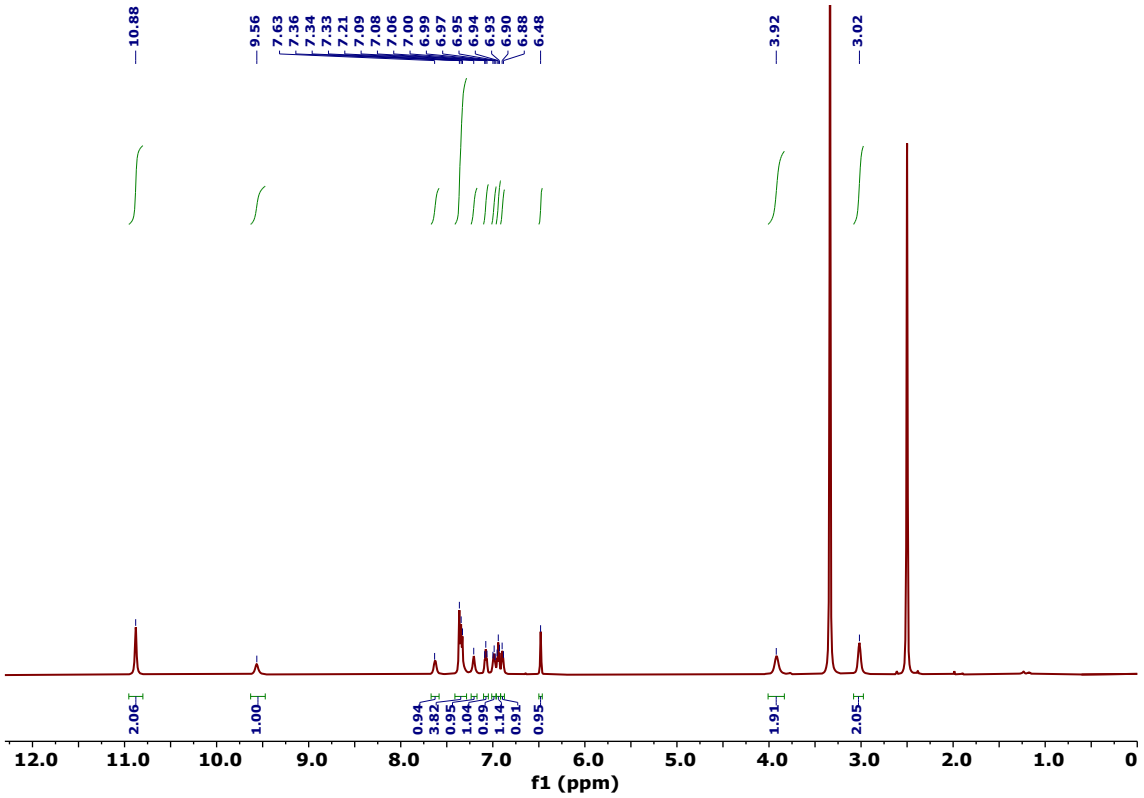


Figure S17. ^{1}H NMR spectrum (600 MHz, DMSO-d_6, 298 K) for compound **L3**.

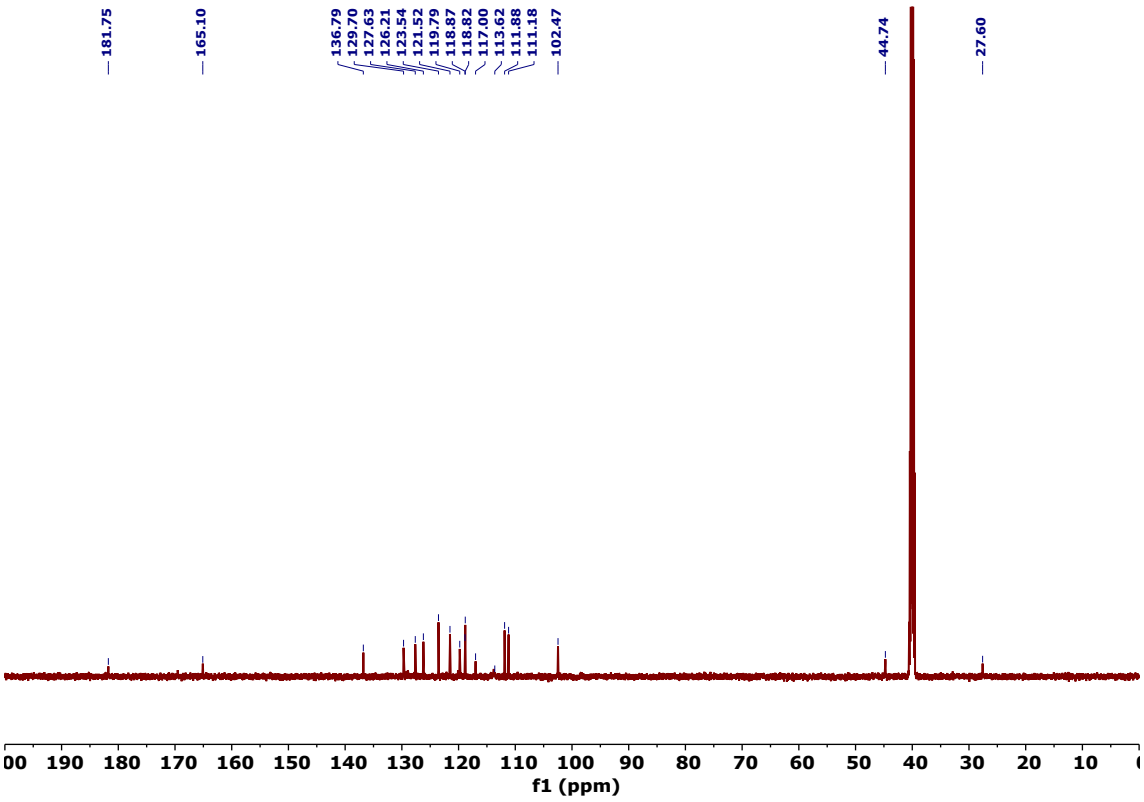


Figure S18. ^{13}C NMR spectrum (151 MHz, DMSO-d_6, 298 K) for compound **L3.**

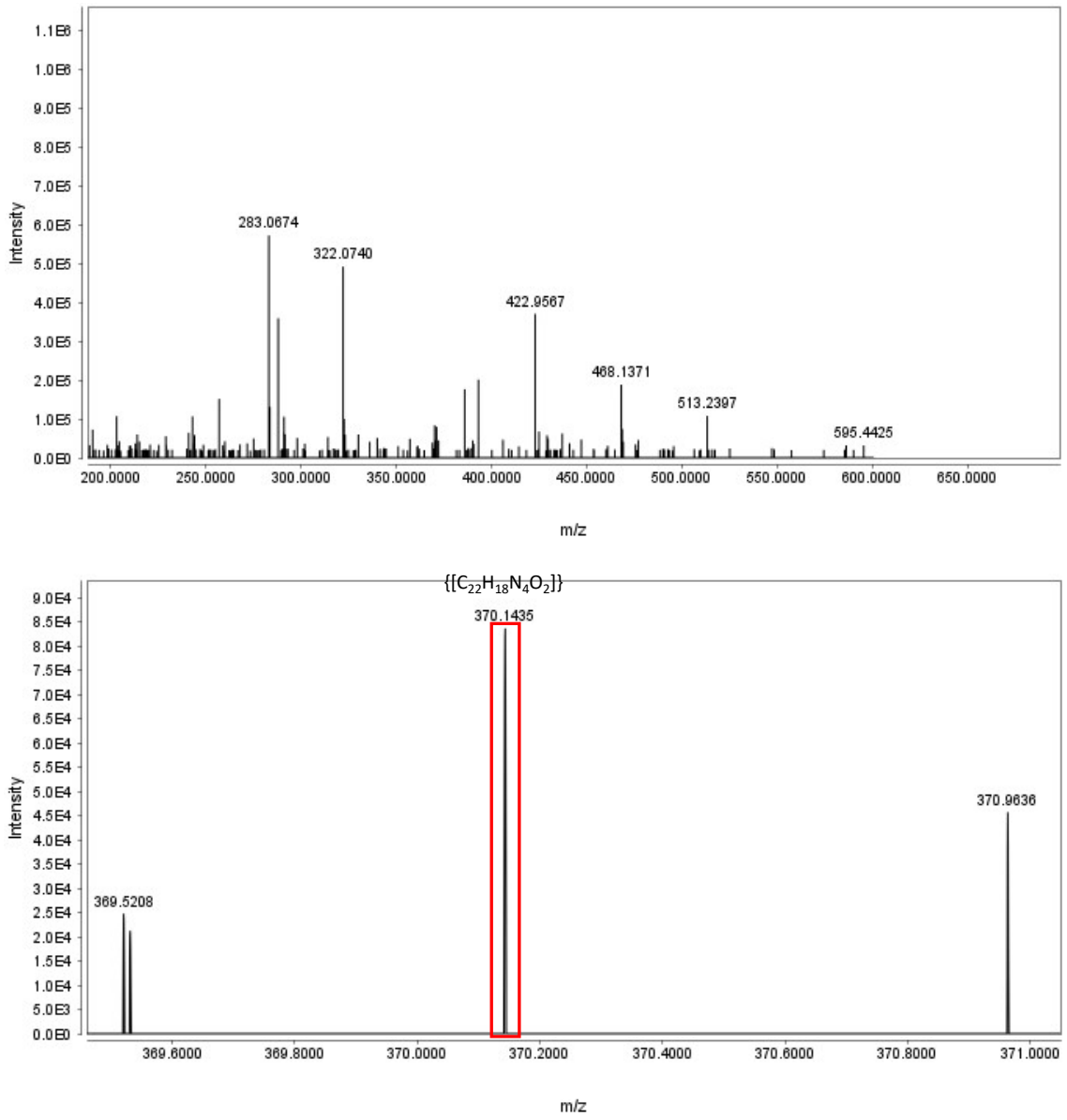
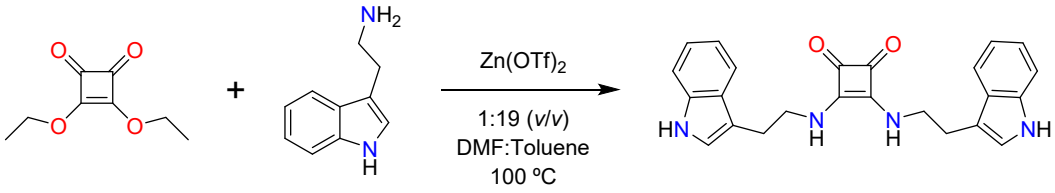


Figure S19. HR-MS (+ESI) spectrum for compound **L3**.

2.3.4. L4



The procedure found in the literature was modified to prepare this compound.[2] To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (200 mg, 1.18 mmol) and zinc(II) trifluoromethanesulfonate (20% mol) in a 1:19 (*v*/*v*) dimethylformamide:toluene mixture (5 mL), tryptamine (395 mg, 2.47 mmol) was added. The solution was heated at 100 °C with stirring for 24 h and, afterwards, it was cooled down to room temperature, which led to the formation of a precipitate that was isolated by filtration. The solid was further washed with methanol (3 × 5 mL) and dried under reduced pressure to remove the residual methanol, collecting the product as a crude white solid. Yield: 380 mg, 0.95 mmol, 81%. ^{1}H NMR (300 MHz, DMSO-d_6, 298 K) δ (ppm): 10.85 (s, 2H, NH), 7.58 (d, *J* = 9.0 Hz, 2H, ArH), 7.39 (s, 2H, NH), 7.33 (d, *J* = 9.0 Hz, 2H, ArH), 7.15 (s, 2H, ArH), 7.05 (t, *J* = 9.0 Hz, 2H, ArH), 6.96 (t, *J* = 9.0 Hz, 2H, ArH), 3.78 (broad, 4H, CH), 2.93 (t, *J* = 6.0 Hz, 4H, CH). ^{13}C NMR (75 MHz, DMSO-d_6, 298 K) δ (ppm): ^{13}C NMR (151 MHz, DMSO-d_6, 298 K) δ (ppm): 182.5, 167.8, 136.3, 127.1, 123.0, 121.0, 118.4, 118.3, 111.4, 110.8, 43.9, 27.2. Elemental analysis: % calc. for $C_{24}H_{22}N_4O_2$ (% found): 72.34 (72.15); H: 5.57 (5.68); N: 14.06 (14.51); O: 8.03 (8.01). HR-MS (+ESI): found *m/z* = 398.1727 [$C_{24}H_{22}N_4O_2$]; calculated *m/z* = 398.1743.

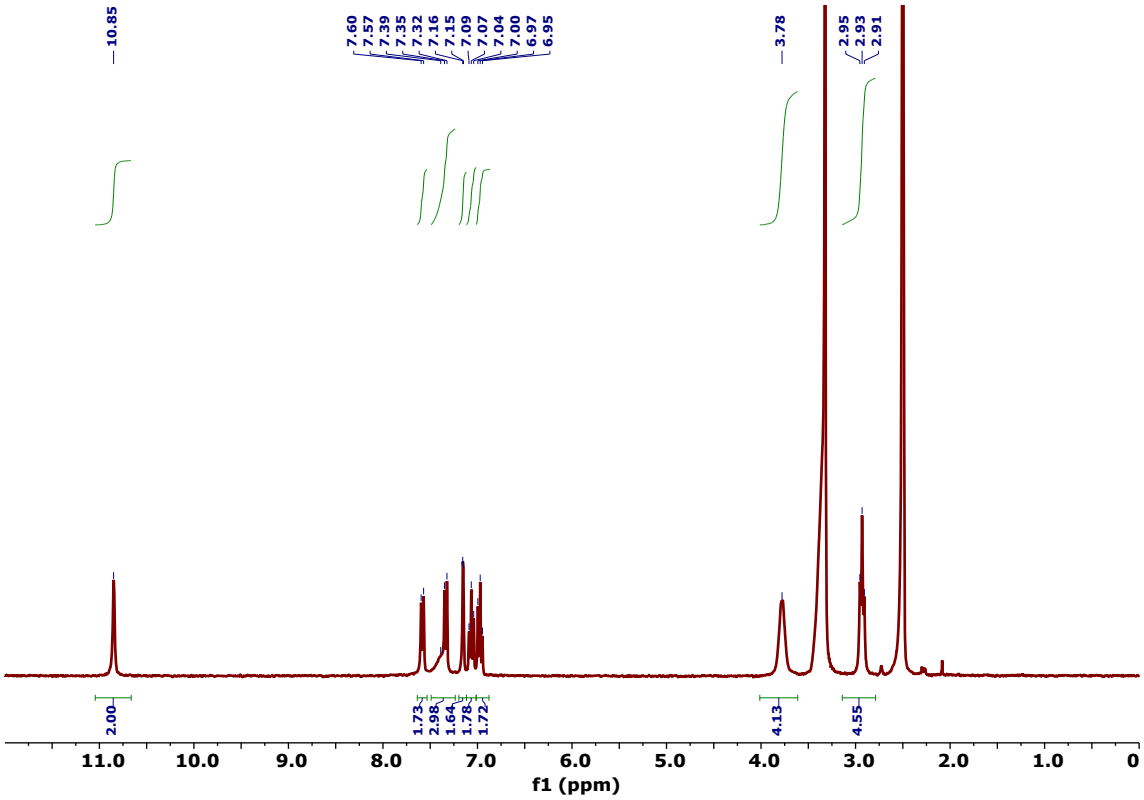


Figure S20. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, 298 K) for compound **L4**.

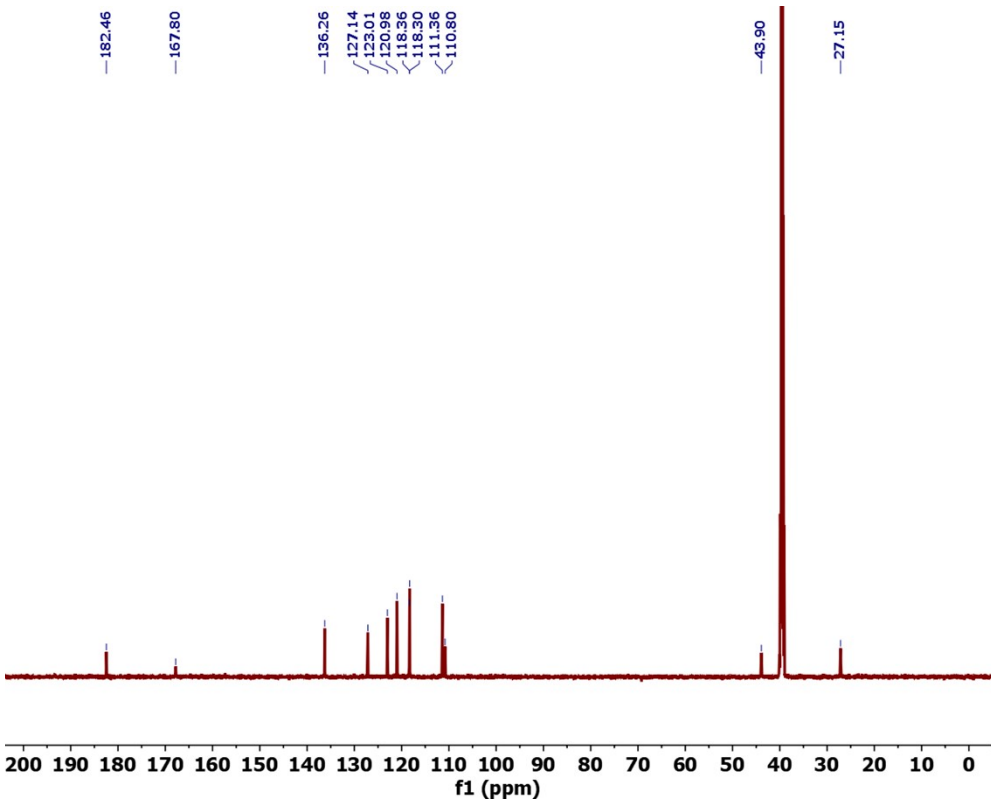


Figure S21. ^{13}C NMR spectrum (151 MHz, DMSO-d_6, 298 K) for compound **L4**.

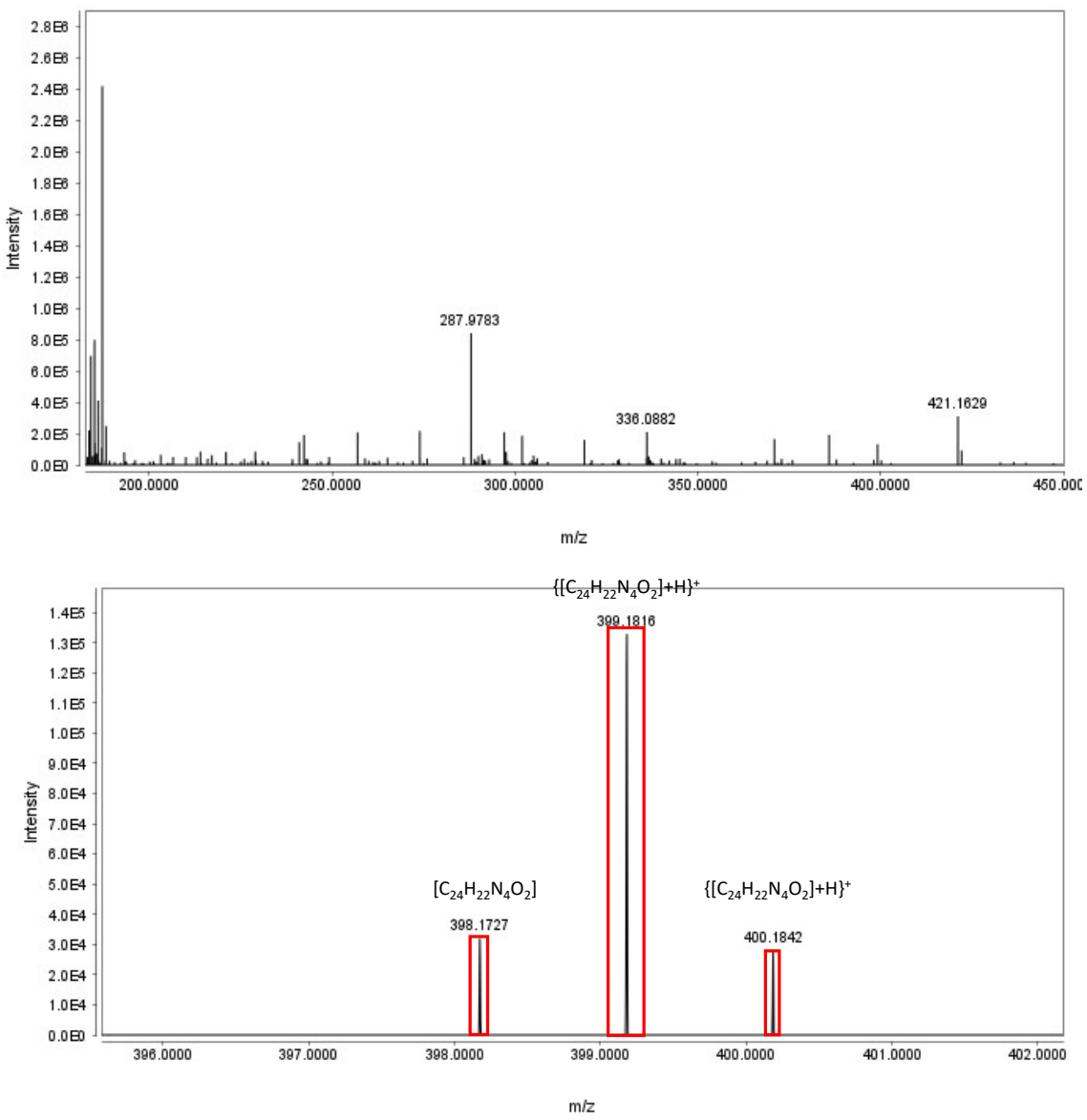
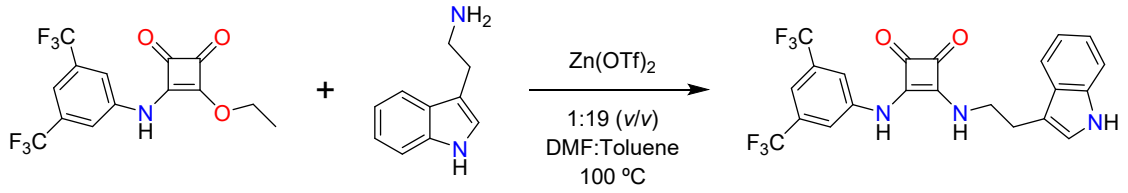


Figure S22. HR-MS (+ESI) spectrum for compound **L4**.

2.3.5. L5



The procedure found in the literature was modified to prepare this compound.[2] To a stirred solution of **intermediate 4** (102 mg, 0.29 mmol) and zinc(II) trifluoromethanesulfonate (10% mol) in a 1:19 (*v*/*v*) dimethylformamide mixture (5 mL) at 100 °C, tryptamine (55 mg, 0.35 mmol) was added. Reaction progress was monitored by TLC chromatography (SiO_2, 1:1 hexane:ethyl acetate). Once completed, the solvent was removed under reduced pressure and the crude was purified by column chromatography (SiO_2, 3:2 hexane:ethyl acetate, 1:1 hexane:ethyl acetate, 1:2 hexane:ethyl acetate). The fractions containing the desired product were combined and the solvent evaporated, collecting it as crude white solid. Yield: 120 mg, 0.26 mmol, 89%. M. p. > 270 °C. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ (ppm): 10.89 (s, 1H, NH), 10.87 (s, 1H, NH), 10.17 (s, 1H, NH), 8.01 (s, 1H, ArH), 7.76 (s, 1H, ArH), 7.63 (d, *J* = 13.0 Hz, 2H, ArH), 7.34 (t, *J* = 8.1 Hz, 1H, ArH), 7.21 (s, 1H, ArH), 7.07 (t, *J* = 7.0 Hz, 1H, ArH), 6.98 (t, *J* = 7.6 Hz, 1H, ArH), 3.94 (q, *J* = 7.5, 6.3 Hz, 2H, CH), 3.02 (t, *J* = 6.1 Hz, 2H, CH). ^{13}C NMR (151 MHz, DMSO-d_6, 298 K) δ (ppm): 185.2, 180.8, 170.3, 162.8, 141.6, 136.8, 131.9 (q, ^{2}J = 35 Hz, CF_3), 127.6, 123.7 (q, ^{1}J = 270 Hz, CF_3), 123.7, 121.5, 118.8, 118.5, 115.1, 111.9, 110.9, 44.9 Elemental analysis: % calc. for $C_{22}H_{15}F_6N_3O_2$ (% found): C: 56.54 (56.42); H: 3.24 (3.18); N: 8.99 (9.12); F: 24.39; O: 6.85 (F + O: 31.28). HR-MS (+ESI): found *m/z* = 467.1034 [$C_{22}H_{15}F_6N_3O_2$]; calculated *m/z* = 467.1068.

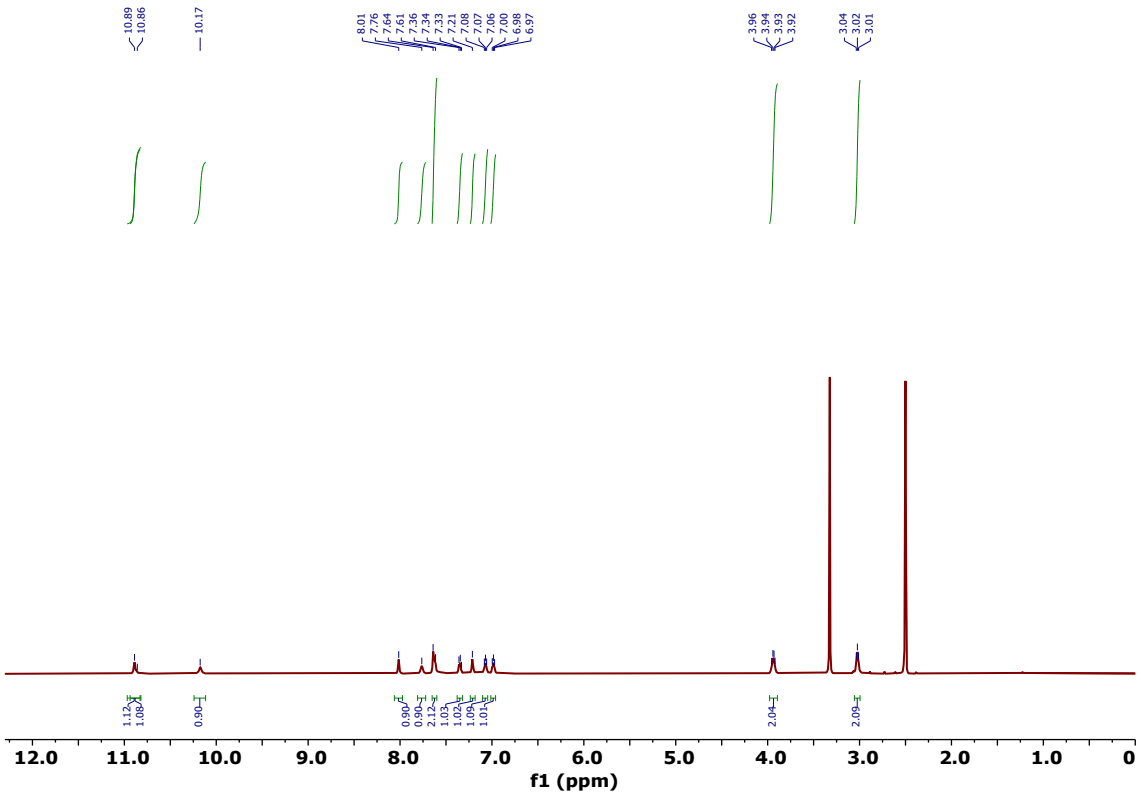


Figure S23. ^{1}H NMR spectrum (600 MHz, DMSO-d_6, 298 K) for compound **L5**.

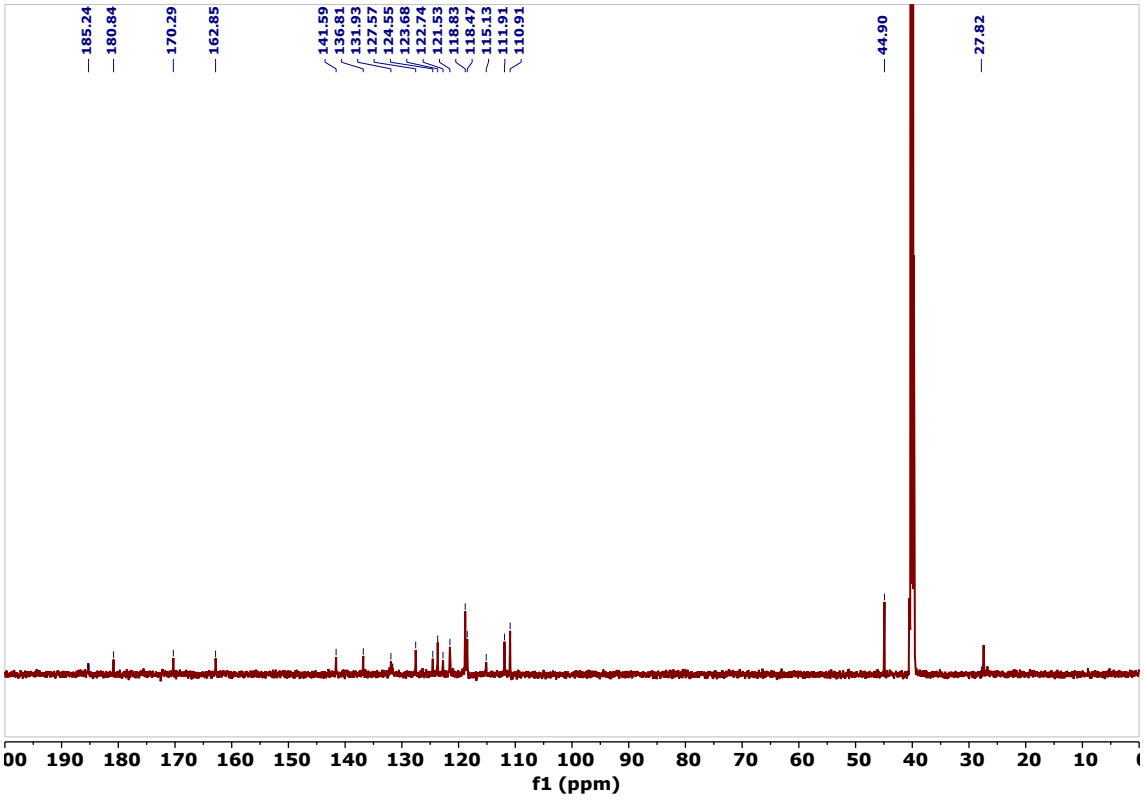


Figure S24. ^{13}C NMR spectrum (151 MHz, DMSO-d_6, 298 K) for compound **L5.**

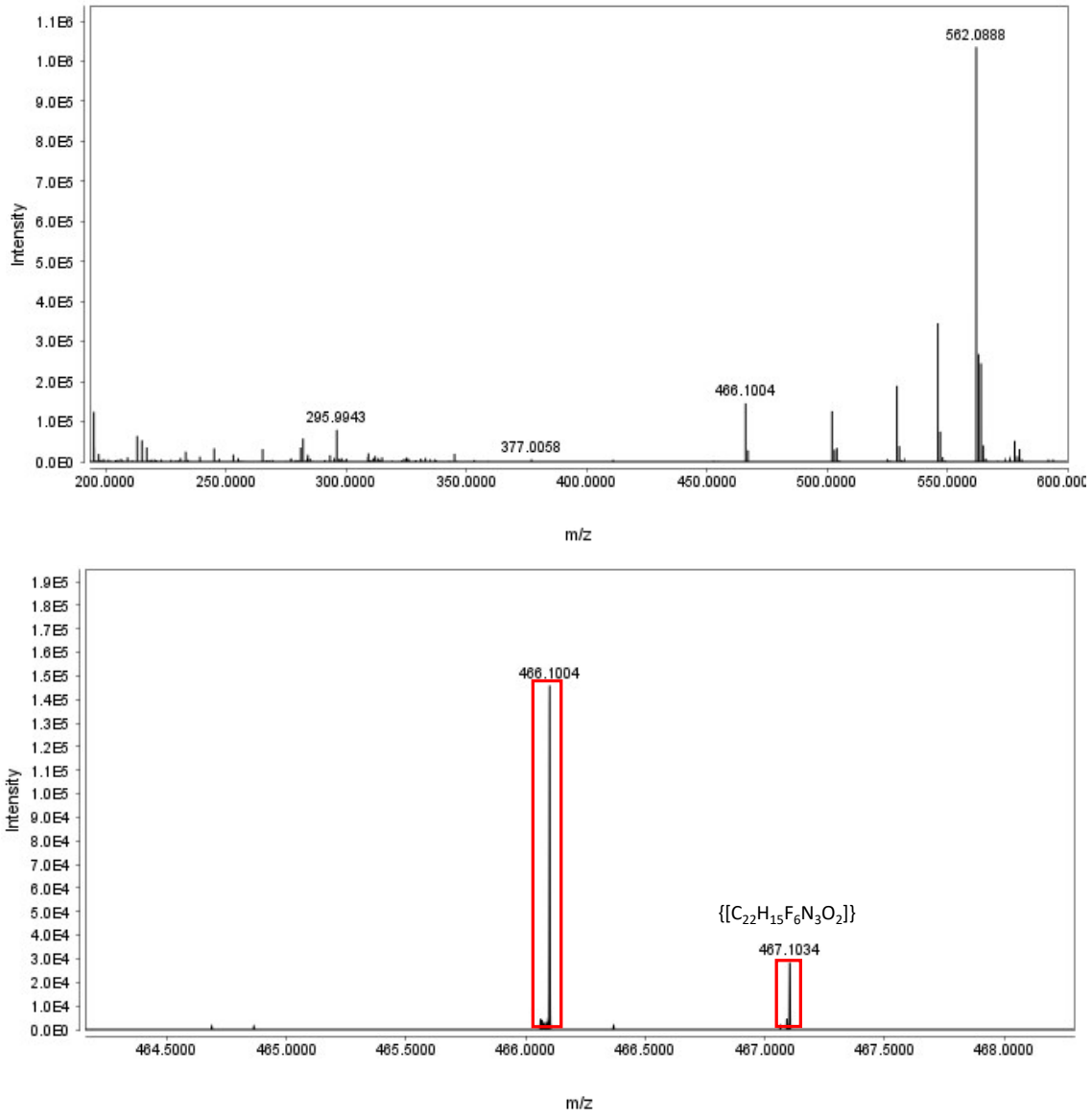
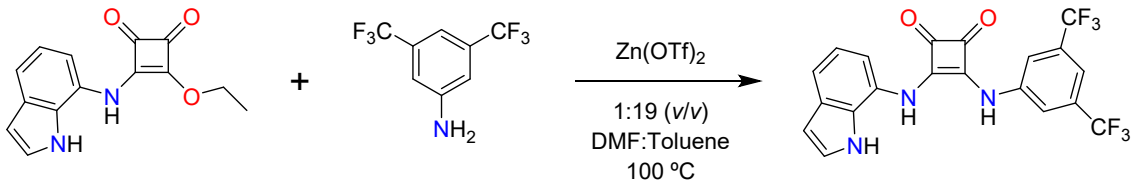


Figure S25. HR-MS (+ESI) spectrum for compound **L5**.

2.3.6. L6



The procedure found in the literature was modified to prepare this compound.[2] To a stirred solution of **intermediate 3** (150 mg, 0.58 mmol) and zinc(II) trifluoromethanesulfonate (20% mol) in a 1:19 (*v*/*v*) dimethylformamide:toluene mixture (5 mL) at 100 °C, 3,5-bis(trifluoromethyl)aniline (148 mg, 0.64 mmol) was added. Reaction progress was monitored by TLC chromatography (SiO_2, 1:1 hexane:ethyl acetate). Once completed, the solvent was removed under reduced pressure. The crude oil was taken up with ethyl acetate and precipitated with hexane. The precipitate was separated by filtration and dried under vacuum; the product was collected as a crude dark green solid. Yield: 140 mg, 0.32 mmol, 54%. M. p. > 300 °C. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ (ppm): 11.03 (s, 1H, NH), 10.15 (s, 1H, NH), 9.99 (s, 1H, NH), 7.95 (s, 2H, ArH), 7.65 (s, 1H, ArH), 7.40 (m, 2H, ArH), 6.97 (d, *J* = 12.0 Hz, 2H, ArH), 6.49 (t, *J* = 6.0 Hz, 1H, ArH). ^{13}C NMR (151 MHz, DMSO-d_6, 298 K) δ (ppm): 183.6, 168.8, 164.7, 141.1, 131.4 (q_t, ^{2}J = 35 Hz, CF_3), 129.9, 129.6, 126.4, 125.1, 124.5, 122.7, 119.6, 119.2, 118.2, 115.7, 115.1, 102.4. Elemental analysis: % calc. for $C_{20}H_{11}F_6N_3O_2$ (% found): C: 54.68 (54.41); H: 2.52 (2.59); N: 9.57 (9.67). HR-MS (+ESI): found *m/z* = 439.0725 [$C_{20}H_{11}F_6N_3O_2$]; calculated *m/z* = 439.0755.

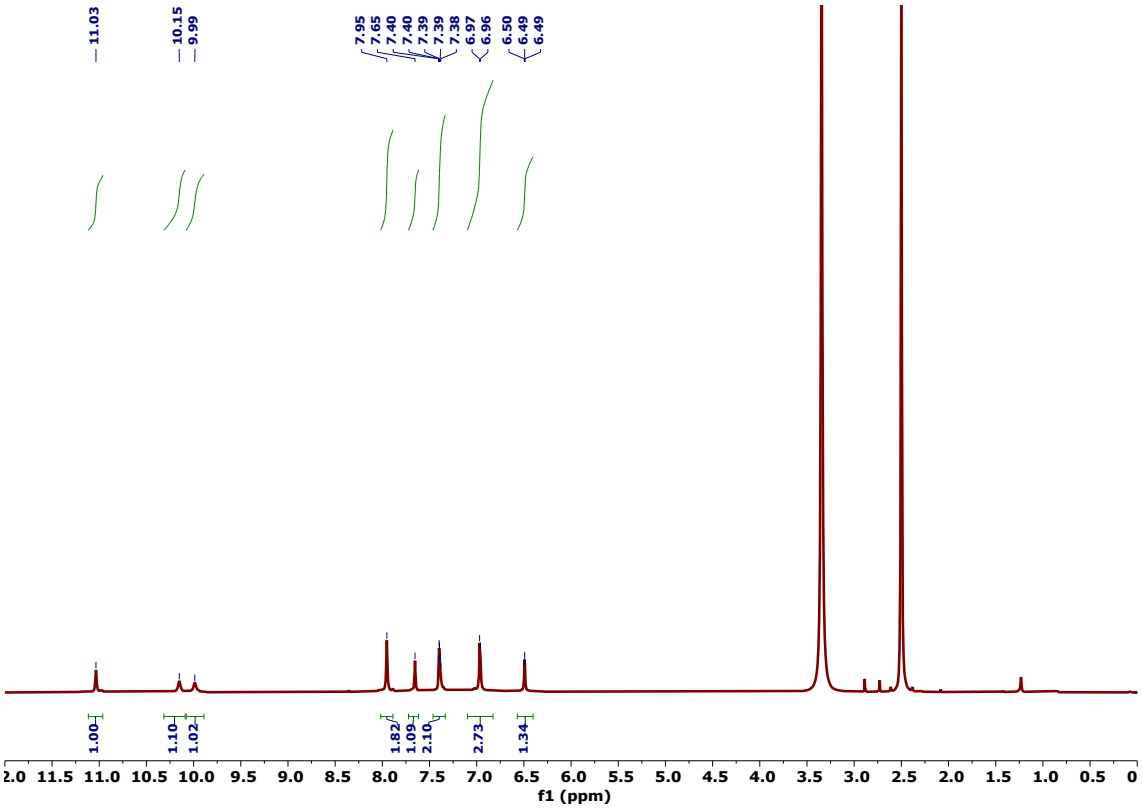


Figure S26. ^{1}H NMR spectrum (600 MHz, DMSO-d_6, 298 K) for compound **L6**.

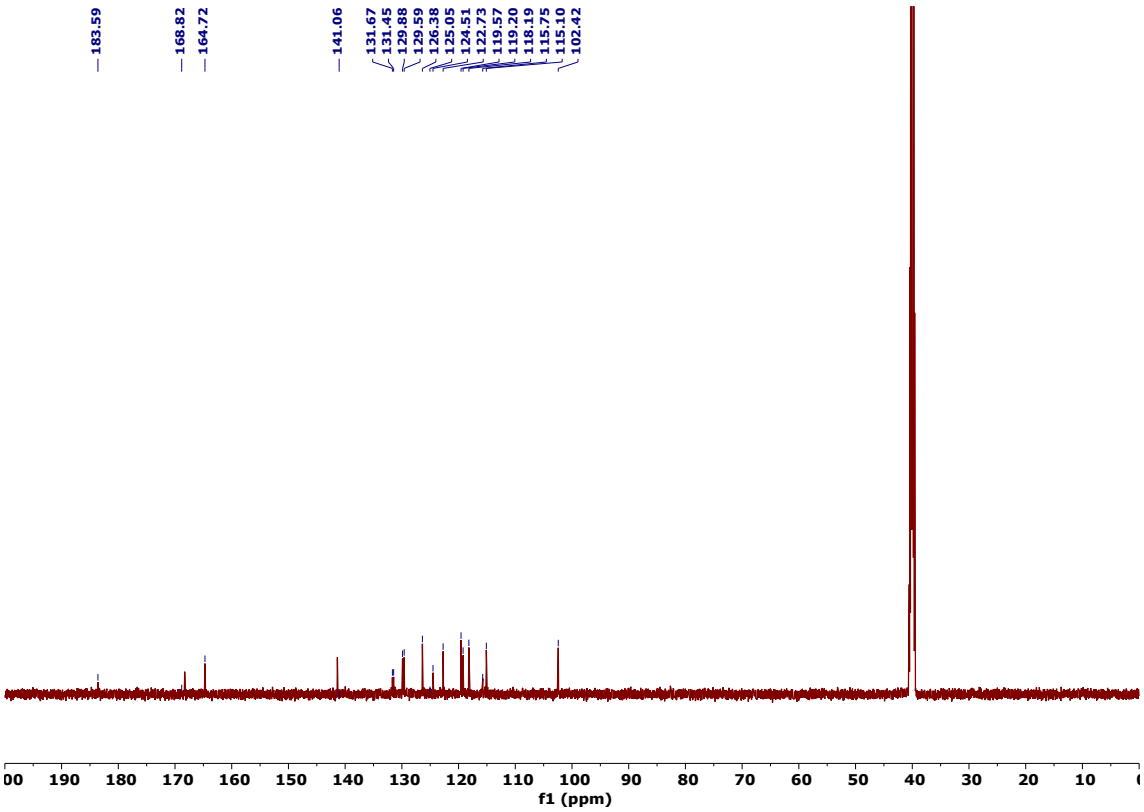


Figure S27. ^{13}C NMR spectrum (151 MHz, DMSO-d_6, 298 K) for compound **L6**.

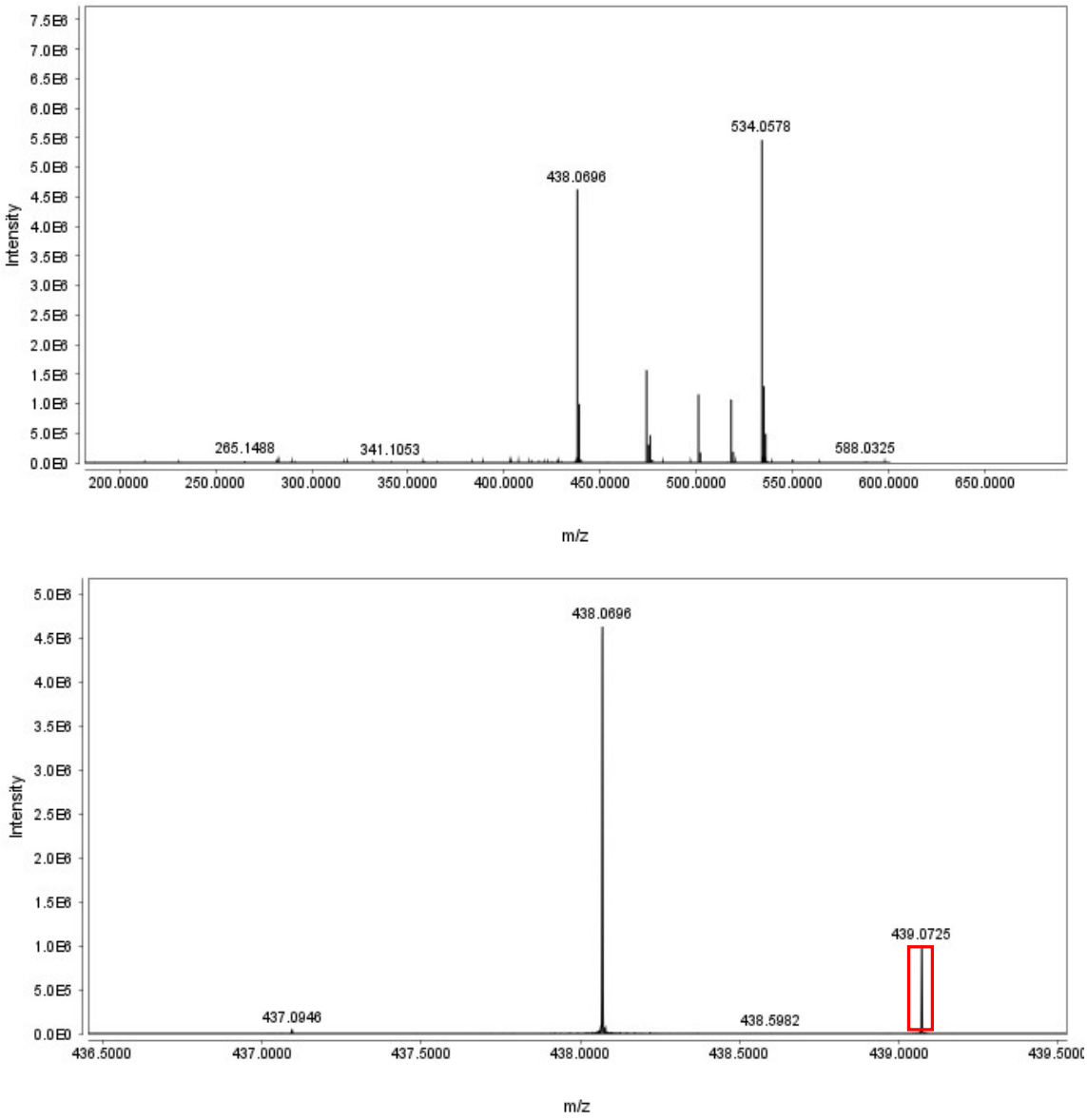
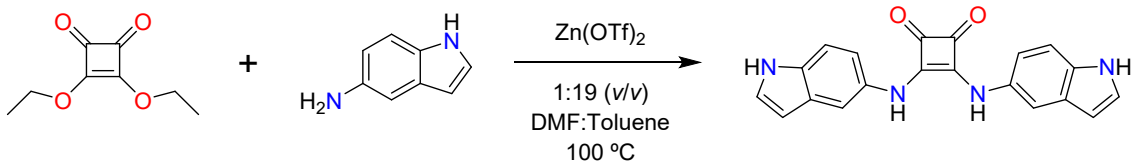


Figure S28. HR-MS (+ESI) spectrum for compound **L6**.

2.3.7. L7



The procedure found in the literature was modified to prepare this compound.[2] To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (250 mg, 1.47 mmol) and zinc(II) trifluoromethanesulfonate (20% mol) in a 1:19 (*v*/*v*) dimethylformamide:toluene mixture (5 mL), 5-aminoindole (427 mg, 3.23 mmol) was added. The solution was heated at 100 °C with stirring for 24 h and, afterwards, it was cooled down to room temperature, which led to the formation of a precipitate that was isolated by filtration. The solid was further washed with methanol (3 × 5 mL) and dried under reduced pressure to remove the residual methanol, collecting the product as a crude white solid. Yield: 400 mg, 1.17 mmol, 80%. M. p. > 266 °C. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ (ppm): 11.09 (s, 2H, NH), 9.69 (s, 2H, NH), 7.70 (s, 2H, ArH), 7.40 (d, *J* = 12.0 Hz, 2H, ArH), 7.36 (broad, 2H, ArH), 7.23 (d, *J* = 12.0 Hz, 1H, ArH), 6.42 (s, 2H, ArH). ^{13}C NMR (151 MHz, DMSO-d_6, 298 K) δ (ppm): 181.5, 165.7, 133.4, 131.4, 128.4, 127.0, 114.3, 112.4, 110.1, 101.7. Elemental analysis: % calc. for $C_{20}H_{14}N_4O_2$ (% found): C: 70.17 (69.98); H: 4.12 (4.01); N: 16.37 (16.82); O: 9.35 (9.19). HR-MS (+ESI): found *m/z* = 342.1123 [$C_{20}H_{14}N_4O_2$]; calculated *m/z* = 342.1117.

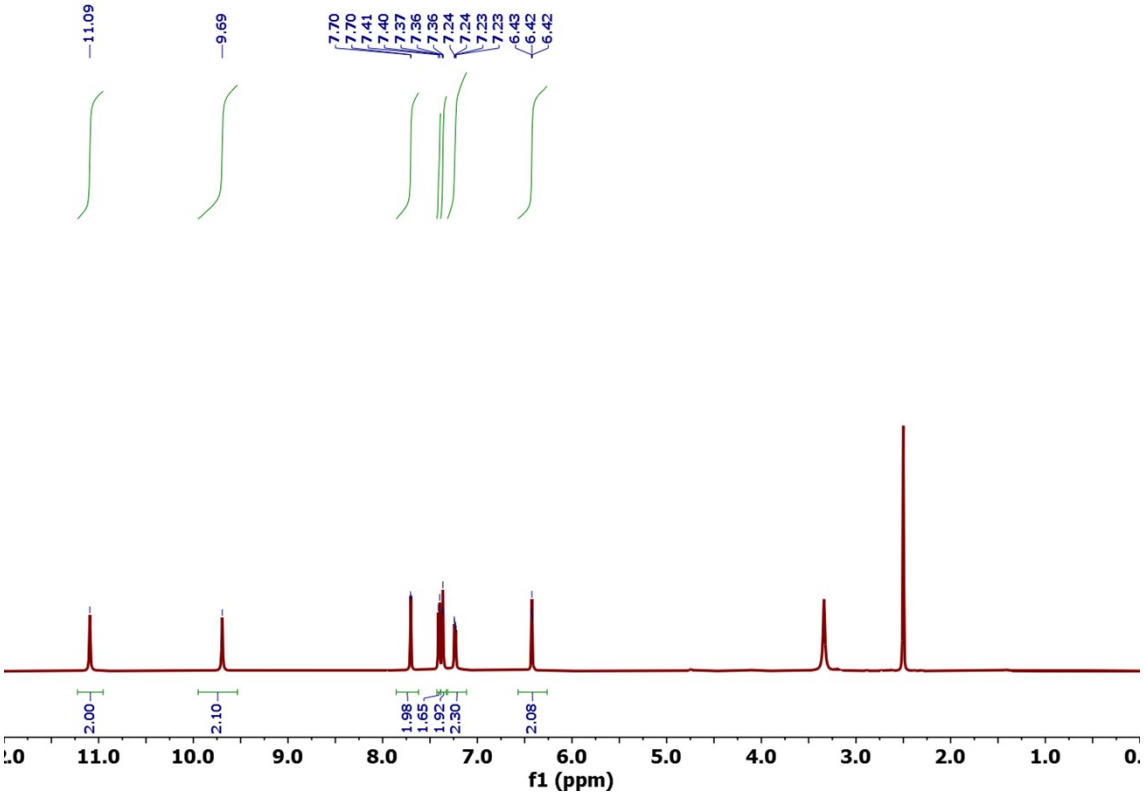


Figure S29. ^{1}H NMR spectrum (600 MHz, DMSO-d_6, 298 K) for compound **L7**.

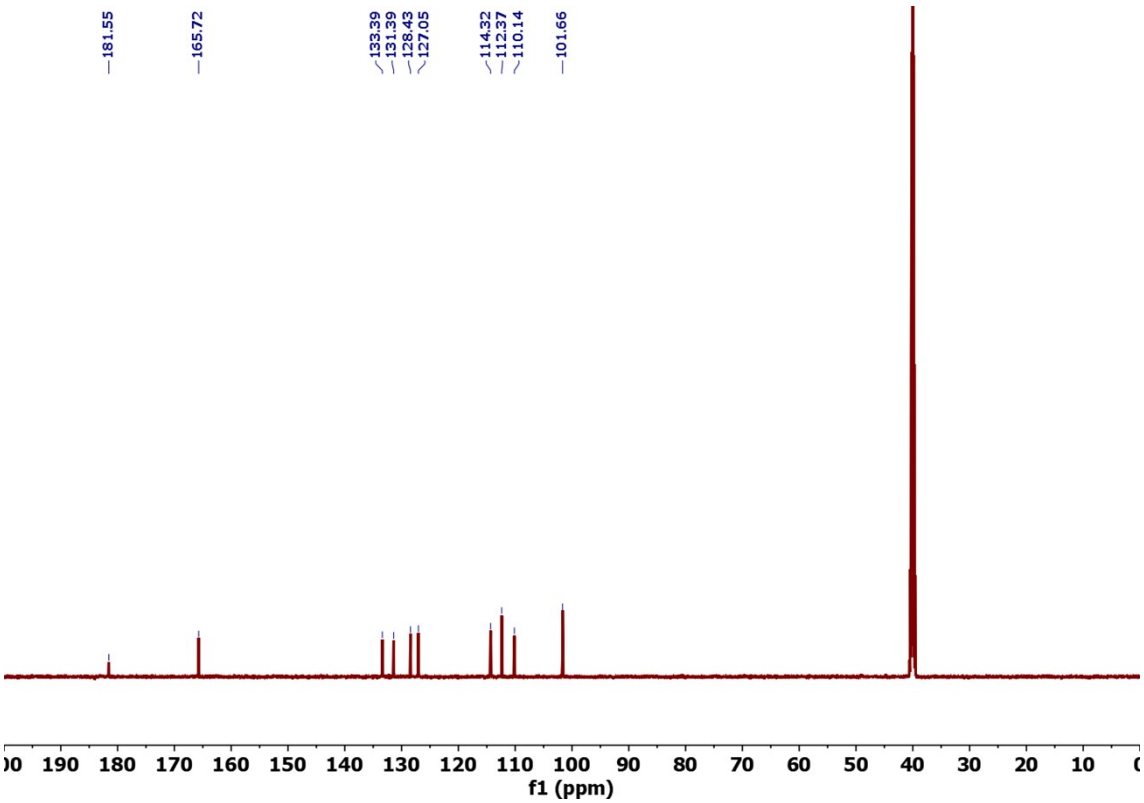


Figure S30. ^{13}C NMR spectrum (151 MHz, DMSO-d_6, 298 K) for compound **L7.**

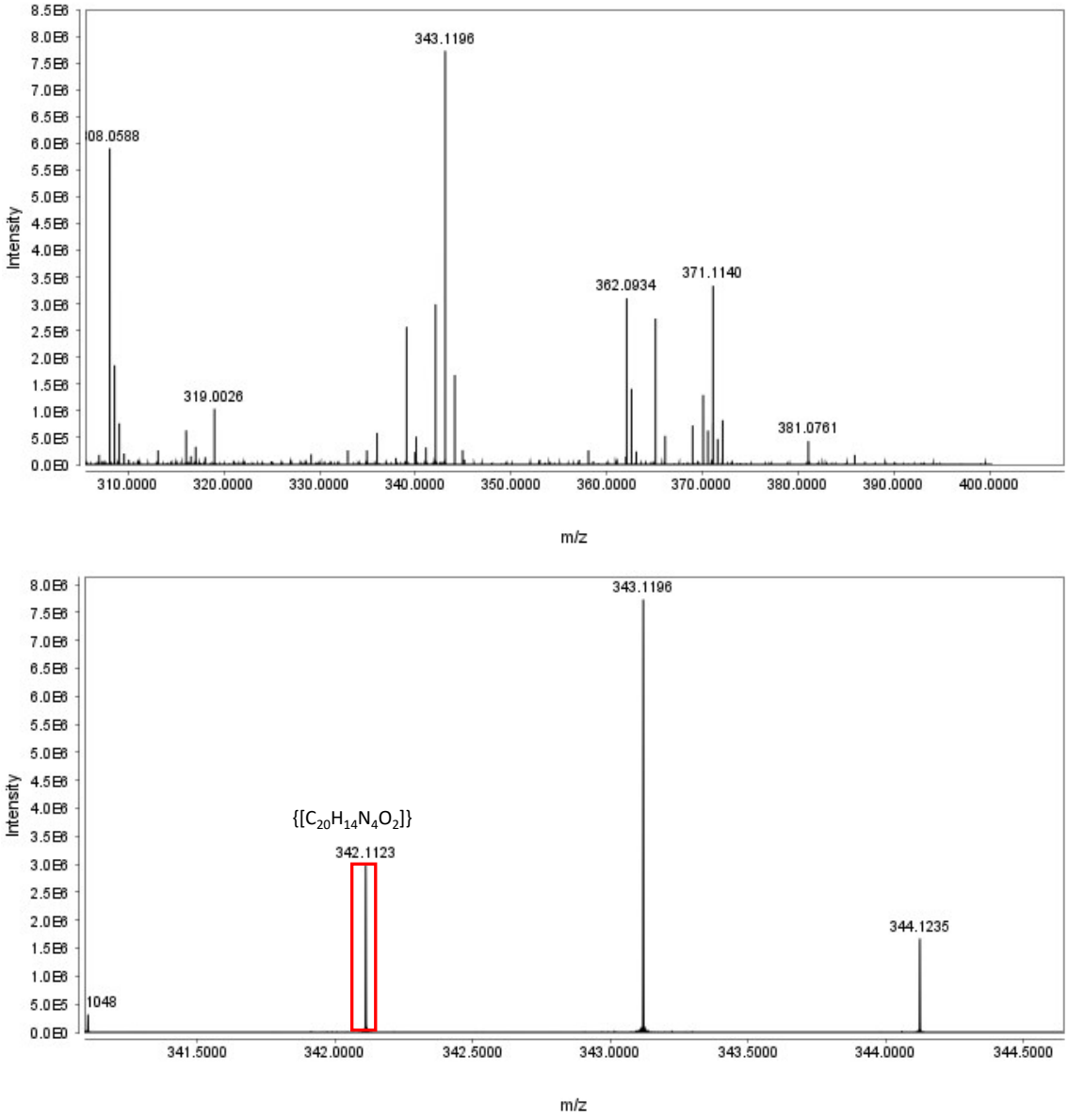
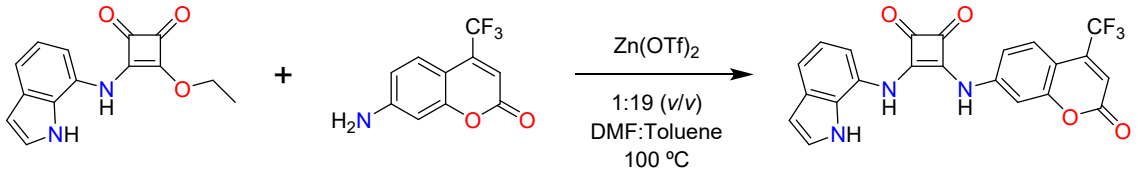


Figure S31. HR-MS (+ESI) spectrum for compound **L7**.

2.3.8. L8



The procedure found in the literature was modified to prepare this compound.[2] To a stirred solution of **intermediate 3** (102 mg, 0.40 mmol) and zinc(II) trifluoromethanesulfonate (10% mol) in a 1:19 (*v*/*v*) dimethylformamide:toluene mixture (5 mL) at 100 °C, 7-amino-4-(trifluoromethyl)coumarin (102 mg, 0.44 mmol) was added. Reaction progress was monitored by TLC chromatography (SiO_2, 1:1 hexane:ethyl acetate). Once completed, the precipitate was separated by filtration and washed with methanol (3 × 5 mL). The solid was further washed with water (10 mL) to remove the residual DMF. The product, collected as a dark green solid, was dried under reduced pressure. Yield: 85 mg, 0.19 mmol, 49%. M. p. > 302 °C. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ (ppm): 11.11 (s, 1H, NH), 10.31 (s, 1H, NH), 9.92 (s, 1H, NH), 7.71 (s, 1H, ArH), 7.65 (d, *J* = 8.2 Hz, 1H, ArH), 7.40 (d, *J* = 6.6 Hz, 2H, ArH), 7.33 (d, *J* = 8.7 Hz, 1H, ArH), 7.02 (d, *J* = 7.4 Hz, 1H, ArH), 6.97 (t, *J* = 7.4 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.49 (s, 1H, ArH). ^{13}C NMR (151 MHz, DMSO-d_6, 298 K) δ (ppm): 168.8, 164.6, 159.1, 155.7, 143.8, 129.8, 126.5, 122.7, 121.3, 119.5, 118.3, 115.9, 115.5, 114.2, 108.2, 106.1, 102.5. Elemental analysis: % calc. for $C_{22}H_{12}F_3N_3O_4$ (% found): C: 60.14 (60.22); H: 2.75 (2.86); N: 9.56 (9.41). HR-MS (+ESI): found *m/z* = 439.0764 [$C_{22}H_{12}F_3N_3O_4$]; calculated *m/z* = 439.0780.

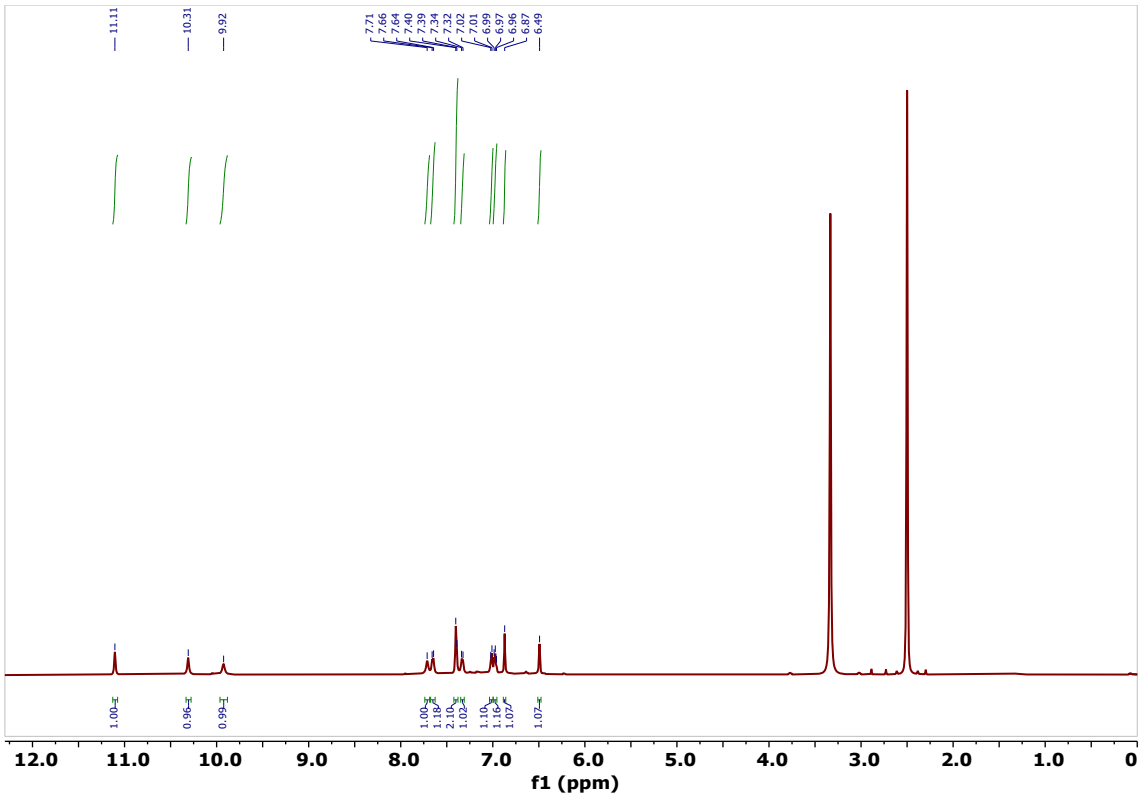


Figure S32. ^{1}H NMR spectrum (600 MHz, DMSO-d_6, 298 K) for compound **L8**.

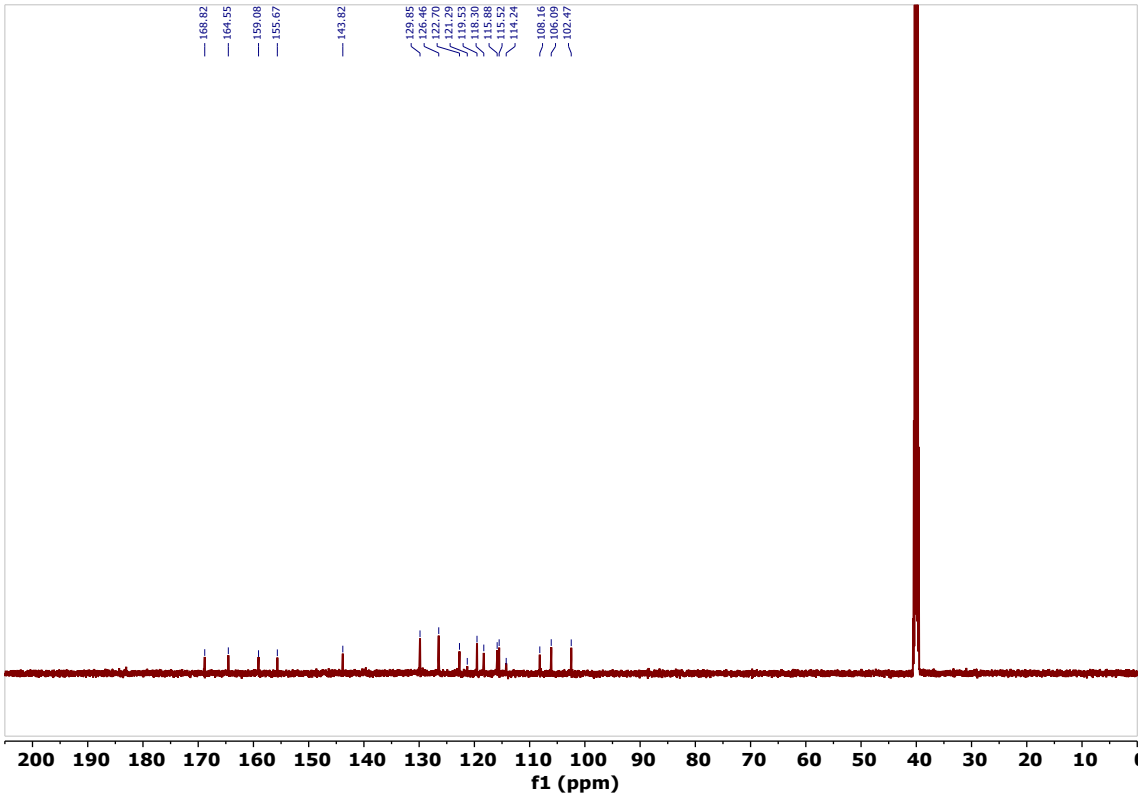


Figure S33. ^{13}C NMR spectrum (151 MHz, DMSO-d_6, 298 K) for compound **L8.**

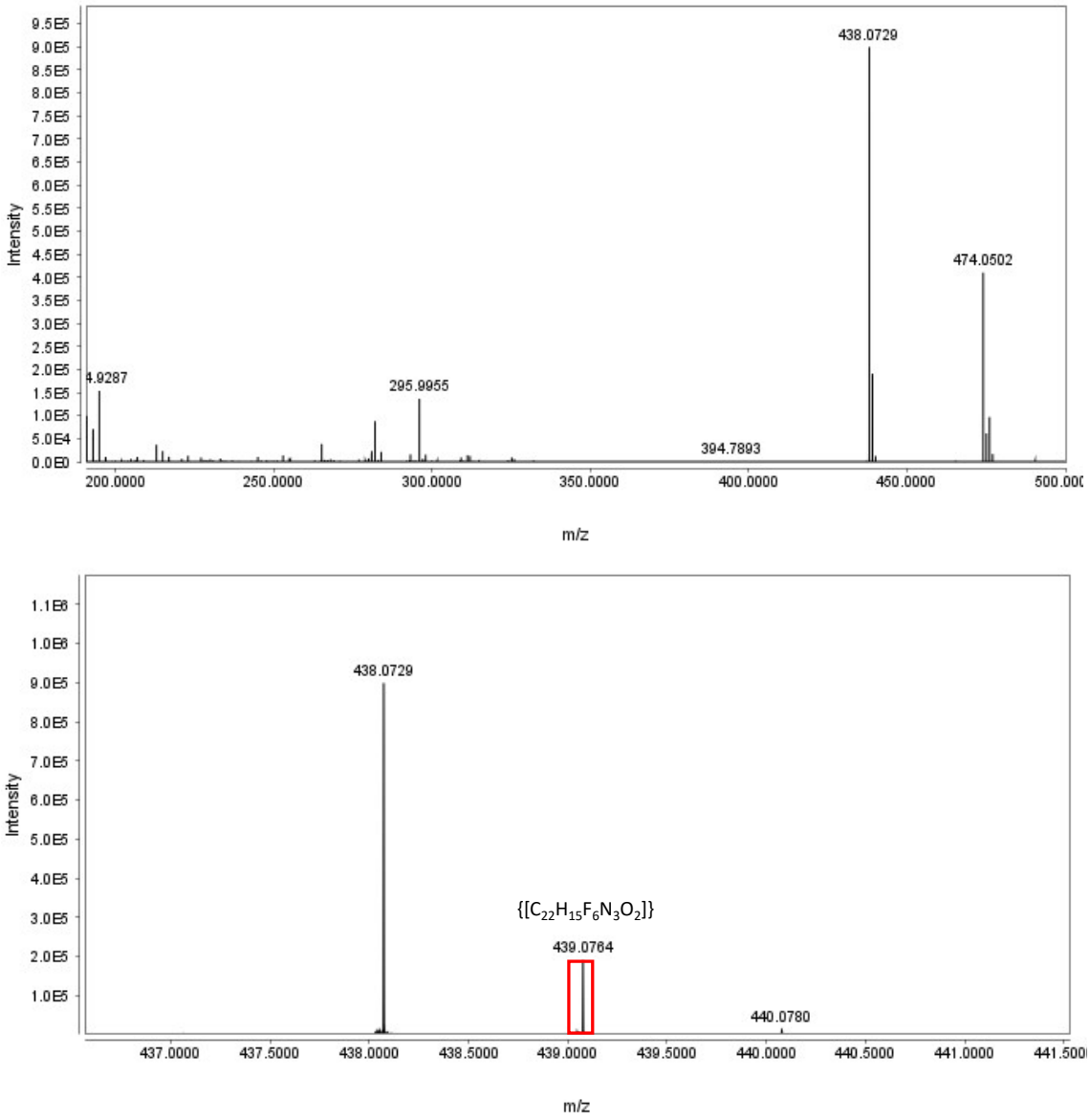


Figure S34. HR-MS (+ESI) spectrum for compound **L8**.

3. X-RAY DIFFRACTION STUDIES

*Solid state structures of compound **L4** and adduct **L6**·TBACl*

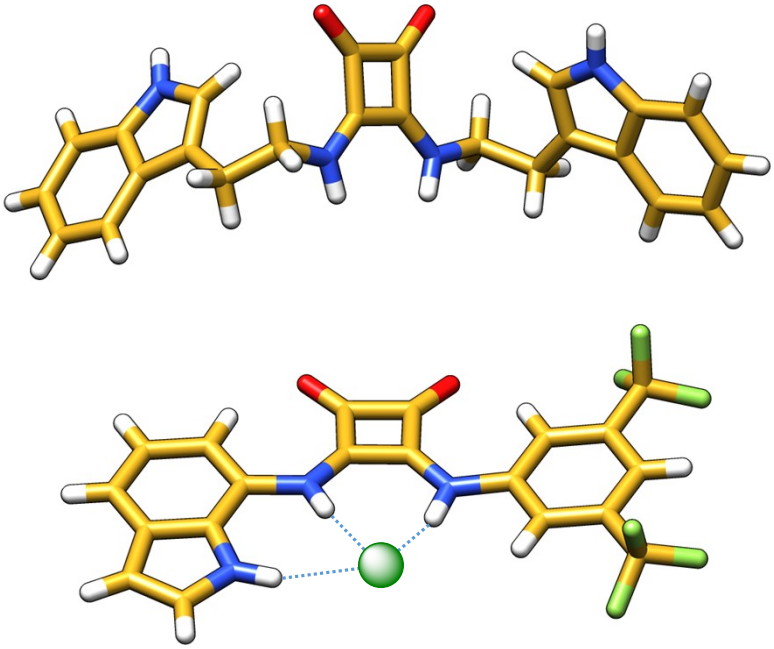


Figure S35. X-ray structures of **L4** (top) and **L6**·TBACl (bottom). In the case of the latter, only one of the two adducts the asymmetric unit is comprised of is shown. A dioxane molecule (**L4**) and a tetrabutylammonium cation (**L6**·TBACl) have been omitted for the sake of simplicity. Intramolecular hydrogen bonds are represented by light blue dotted lines.

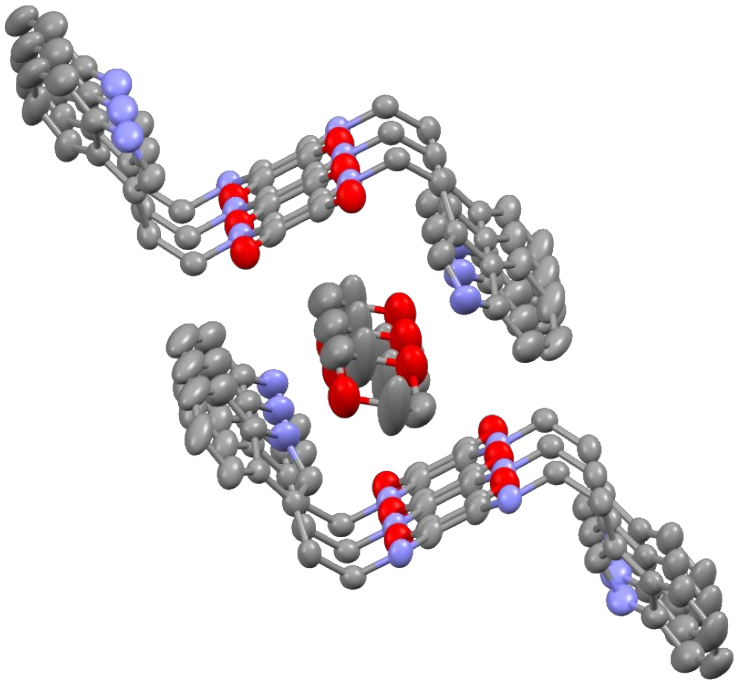


Figure S36. View of the molecular structure of **L4** across the *b* crystallographic axis. Hydrogen atoms have been omitted for the sake of simplicity.

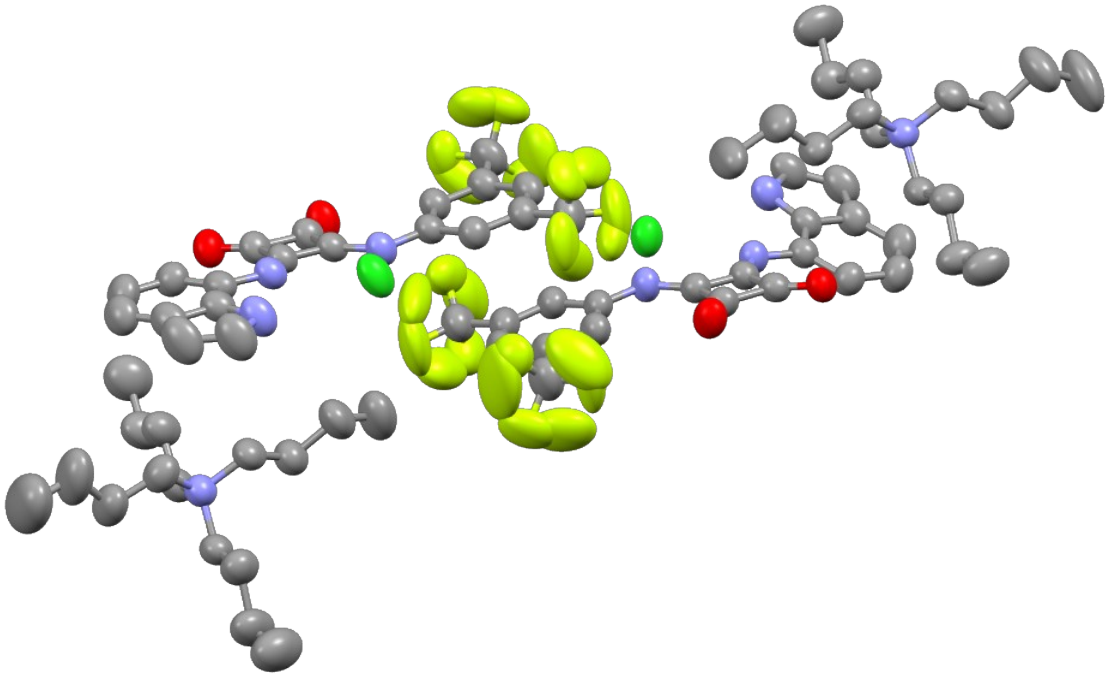


Figure S37. View of the asymmetric unit of **L6**·TBACl. Hydrogen atoms have been omitted for the sake of simplicity.

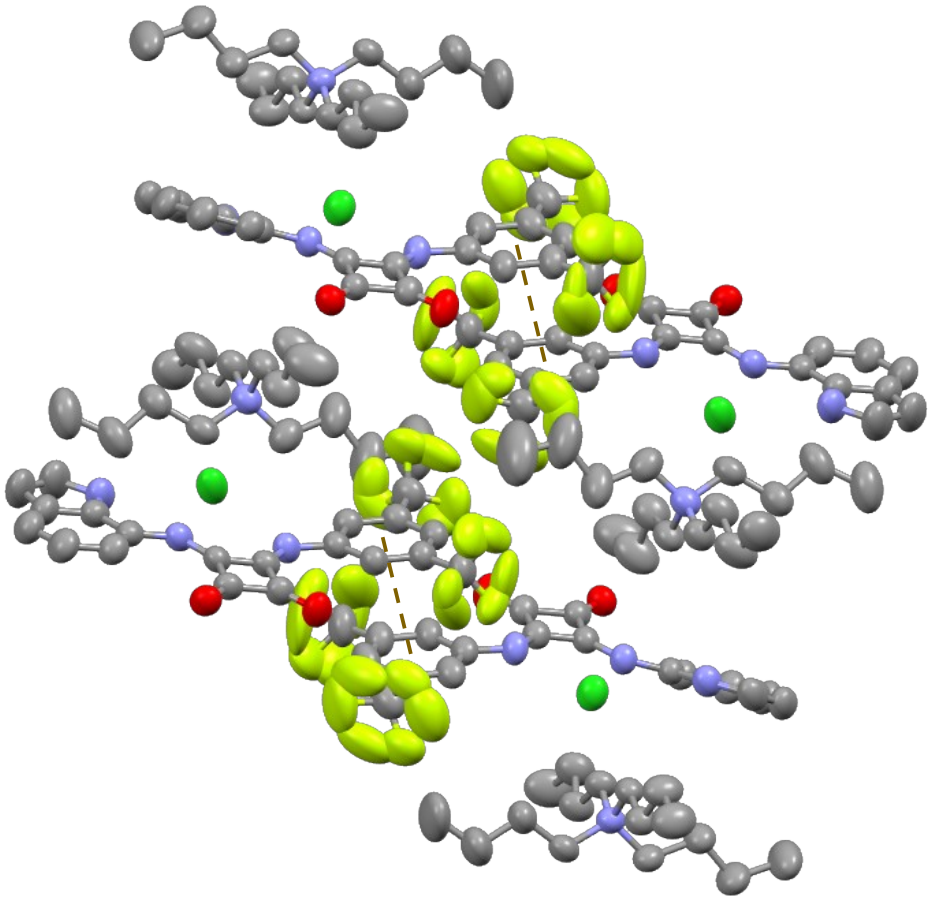


Figure S38. View of the crystal packing of **L6**·TBACl. Hydrogen atoms have been omitted for the sake of simplicity. π-stacking interactions are represented by brown dotted lines.

Table S1. Hydrogen bond distances (Å) and angles (°) for **L6**·TBACl involving the chloride anion (X = N or C).

Involved atoms	X···Cl distance	X-H-Cl angle
N(1)-H(1)···Cl(1)	3.221	163.31
N(2)-H(2)···Cl(1)	3.189	173.45
N(3)-H(3)···Cl(1)	3.161	158.43
C(18)-H(18)···Cl(1)	3.835	135.17
N(4)-H(4)···Cl(2)	3.311	146.20
N(5)-H(5)···Cl(2)	3.159	168.27
N(6)-H(6)···Cl(2)	3.182	168.18
C(34)-H(34)···Cl(2)	3.925	135.68

Table S2. Crystal data and refinement details for **L4** and **L6**·TBACl.

	L4	**L6**·TBACl
Empirical formula	$C_{24}H_{22}N_4O_2 \cdot C_4H_8O_2$	$C_{36}H_{47}ClF_6N_4O_2$
MW	486.56	717.23
crystal system	Monoclinic	Triclinic
space group	*C*2/c	*P*-1
T/K	298(2)	240(2)
a/Å	23.691(4)	16.7881(5)
b/Å	6.0862(9)	16.8007(5)
c/Å	18.277(3)	17.4748(5)
α/deg	90	94.201(2)
β/deg	107.034(12)	112.935(2)
γ/deg	90	119.085(1)
V/Å^3	2519.7(7)	3749.5(2)
F(000)	1032	1512
Z	8	8
λ, Å	1.54178	1.54178
D_{calc}/g cm^{-3}	1.283	1.271
μ/mm^{-1}	0.706	1.472
θ range/deg	3.90–64.31	2.90–66.73
R_{int}	0.0748	0.0754
reflections measured	2646	101170
unique reflections	1537	13224
reflections observed	1126	7627
GOF on F^2	1.184	1.066
$R1^a$	0.0951	0.0703
$wR2^b$	0.3177	0.2541
Largest ≠ peak & hole/eÅ^{-3}	0.274 and -0.272	0.405 and -0.368

^{a} $R1 = \sum ||F_0| - |Fc|| / \sum |F_0|$. ^{b} w$R2$ (all data) = $\{\sum[w(|F_0|^2 - |Fc|^2)^2]/\sum[w(F_0^4)]\}^{1/2}$

Slow evaporation of a dioxane solution of **L4** provided colourless single crystals. The asymmetric unit comprises half a molecule of receptor and half a molecule of dioxane (Fig. S36). The squaramide adopts a chair-like disposition and each one establishes hydrogen-bonding interactions with two neighbouring squaramides and two dioxane molecules: the former involves the C=O and N-H groups of the squaramide core (N···O 2.815 Å, N-H-O 154.88°), while the latter implies the indoles' N-H fragment and one of the dioxane's oxygen atoms (N···O 2.921 Å, N-H-O 147.77°); the strength of both hydrogen bonds can be regarded as moderate. If seen across the *b* edge of the unit cell, dioxane molecules find themselves in the middle of a pseudo-cavity generated by the surrounding squaramide molecules (Fig. S36).

Single crystals of **L6**·TBACl were obtained by slow evaporation of a *n*-butanol solution containing **L6** and two equivalents of tetrabutylammonium chloride.

Three-dimensional X-ray data were collected on a Bruker D8 VENTURE diffractometer. Data were corrected for absorption effects using the multi-scan method (SADABS).[4] Complex scattering factors were taken from the SHELXL-2016[5] programme running under the Olex2 programme.[6] Both structures were solved with SHELXT[7] and refined by full-matrix least-squares on F^2. All hydrogen atoms were included in calculated positions and refined in riding mode. The structure of **L6**·TBACl shows positional disorder for the four trifluoromethyl groups, with the following occupation factors: 0.42(3) (F1, F2 and F3), 0.54(3) (F4, F5 and F6), 0.47(3) (F7, F8 and F9) and 0.46(2) (F10, F11 and F12); EXTI correction was used to complete the refinement. In both cases refinement converged with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen bond distances and angles for **L6**·TBACl involving chloride, and crystal data and details on data collection and refinement for both structures, are summarised in **Tables S1** and **S2**, respectively. Both of them were drawn with the UCSF Chimera software[8] and Mercury. It is important to remark that the crystal of **L4** diffracts weakly, which generates two alerts (A and B) in the checkCIF/PLATON report that have been properly justified.

4 SADABS: L. Krause, R. Herbst-Irmer, G. M. Sheldrick and D. Stalke, *J. Appl. Cryst.*, 2015, **48**, 3-10.
5 SHELXL: G. M. Sheldrick, *Acta Cryst*., 2008, **A64**, 112-122.
6 Olex2: O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339-341.
7 SHELXT: G. M. Sheldrick, *Acta Cryst.*, 2015, **A71**, 3-8.
8 UCSF Chimera: E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng and T. E. Ferrin, *J. Comput. Chem.*, 2004, **25**, 1605-1612.

4. ^{1}H NMR TITRATIONS

4.1. Titration procedure and titration data fitting

2 mL of a DMSO-d_6/0.5% water stock solution of the corresponding squaramide (host) were prepared (0.005 or 0.01 M). From this solution, 1 mL was taken to prepare the solution of the titrating agent (guest; tetrabutylammonium chloride or tetrabutylammonium nitrate); in this way the dilution effect is avoided. 0.5 mL of the solution of the host were put into an NMR tube, which was capped with a septum, and the ^{1}H NMR spectrum was recorded. Subsequently, an aliquot of the solution of the guest was added with a proper microsyringe through the septum; the solution was then homogenised and the spectrum recorded. This process was repeated several times.

For each ^{1}H NMR titration, the signals of the protons of the NH groups of the molecules were monitored for changes in chemical shift, which provided several data sets that were employed in the determination of the association constants K_a. The fitting was performed with the WinEQNMR2 software.[9] When possible, data were fitted satisfactorily to the 1:1 (L:A) binding model, L being the receptor and A the anion (chloride or nitrate).

[9] M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311-312.

4.2. ^{1}H NMR titration spectra and fitted binding isotherms

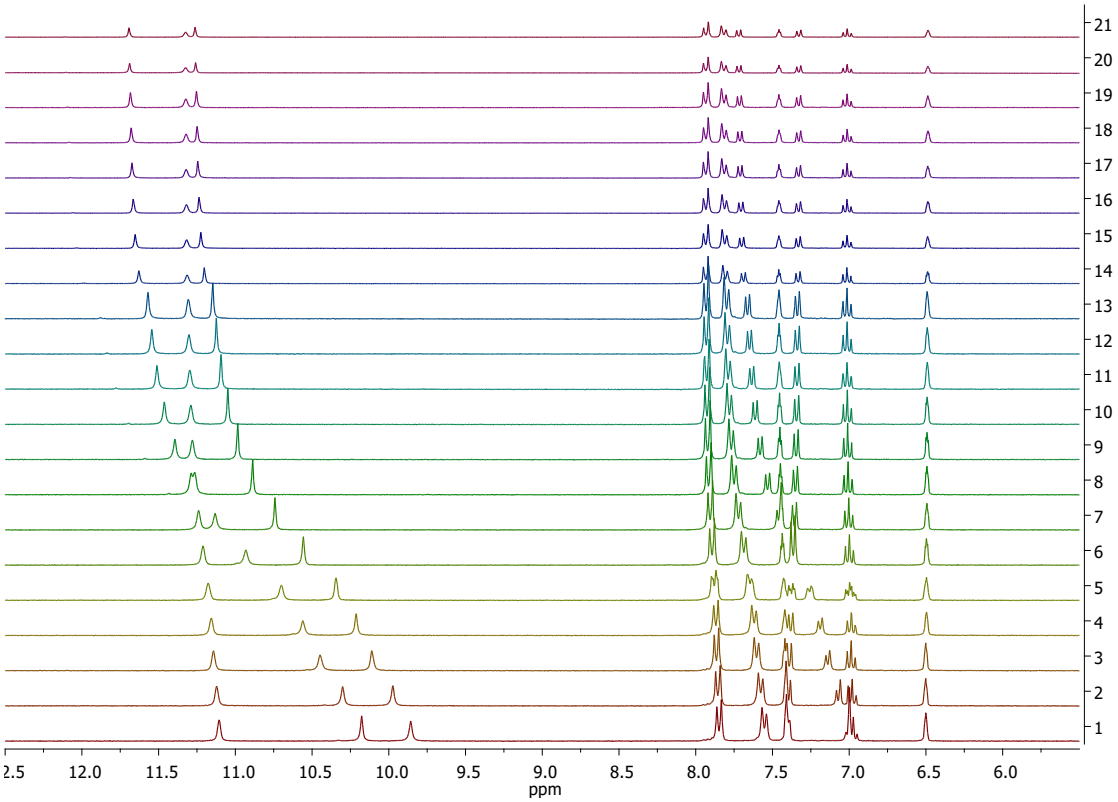


Figure S39. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.2 M solution of TBACl, prepared with a 0.01 M solution of **L1**, to a 0.01 M solution of **L1**.

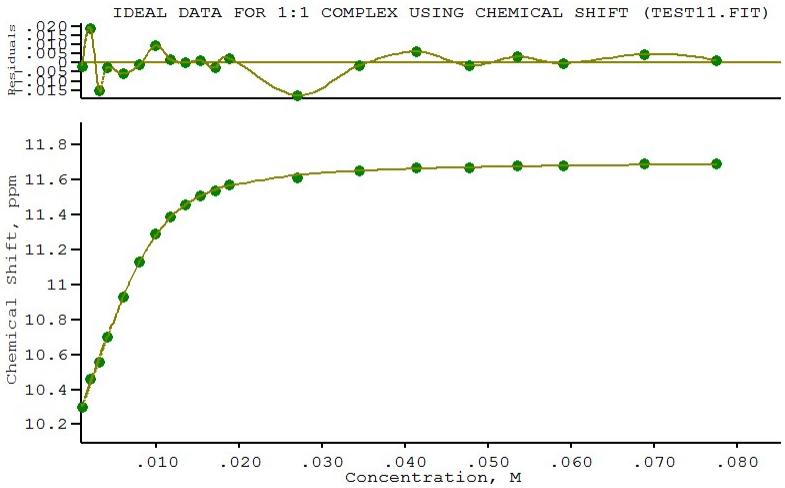


Figure S40. Fitted binding isotherm obtained for the titration of a 0.01 M solution of compound **L1** with a 0.2 M solution of TBACl (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 1013 ± 26 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 16:28:59 on 02/01/2018

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes. October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	1.01319E+03	2.000E-01	2.597E+01	2.027E+00	K1
2	1	1.01589E+01	2.000E-01	5.338E-03	1.292E+00	SHIFT Sn
3	1	1.17097E+01	1.000E+00	3.067E-03	1.788E+00	SHIFT Sn(L)

0RMS ERROR = 8.17E-03 MAX ERROR = 1.89E-02 AT OBS.NO. 2
RESIDUALS SQUARED = 1.13E-03
RFACTOR = 0.0665 PERCENT

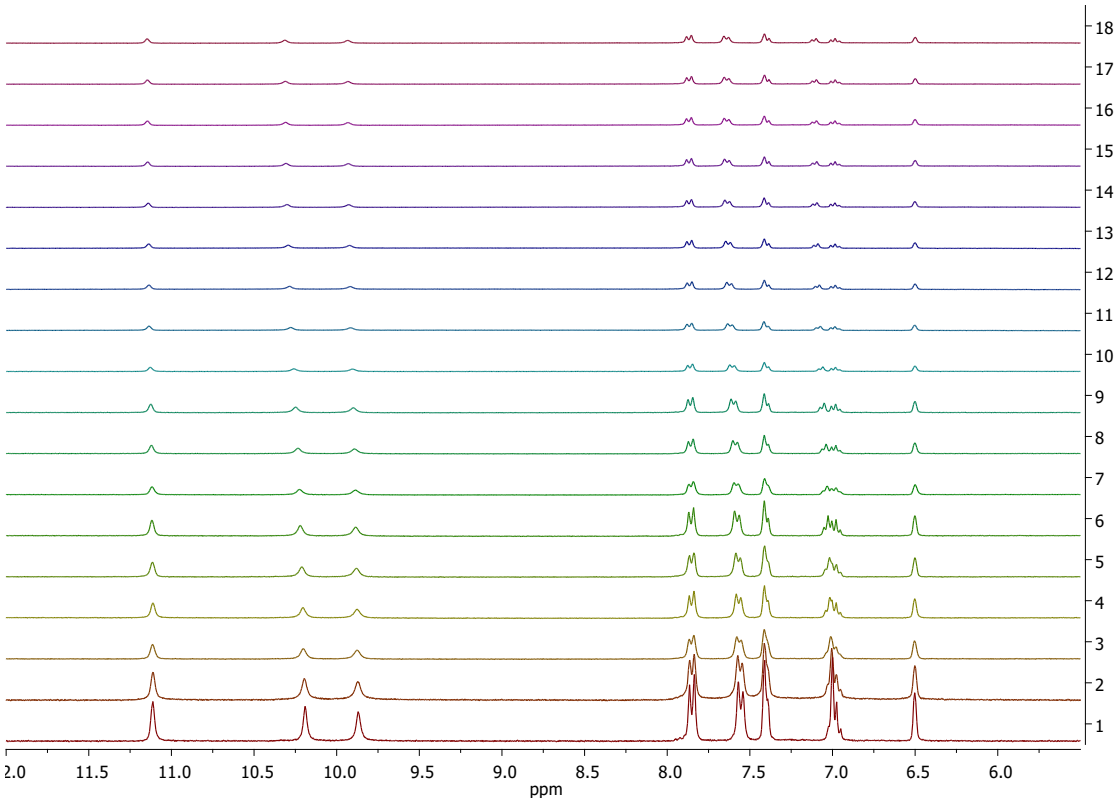


Figure S41. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.6 M solution of $TBANO_3$, prepared with a 0.01 M solution of **L1**, to a 0.01 M solution of **L1**.

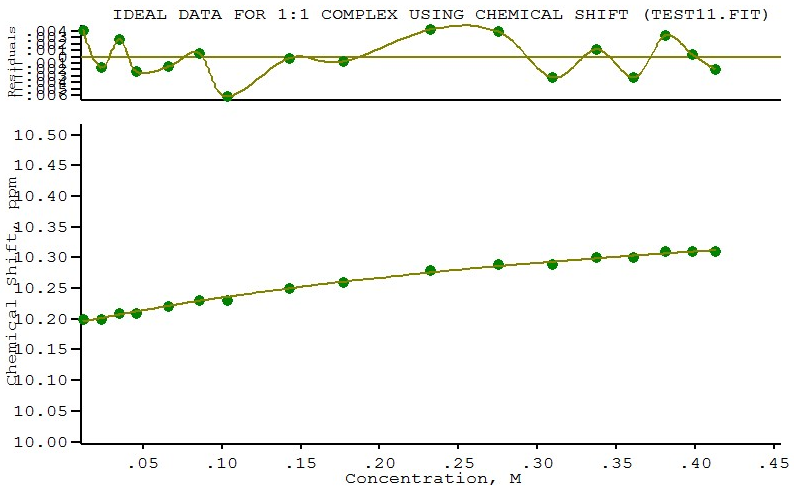


Figure S42. Fitted binding isotherm obtained for the titration of a 0.01 M solution of compound **L1** with a 0.6 M solution of $TBANO_3$ (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 2.2 ± 0.4 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 18:12:39 on 02/15/2018

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes. October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	2.17014E+00	2.000E-01	3.972E-01	1.288E+02	K1
2	1	1.01882E+01	2.000E-01	2.443E-03	5.479E+00	SHIFT Sn
3	1	1.04496E+01	1.000E+00	2.529E-02	1.002E+02	SHIFT Sn(L)

0RMS ERROR = 3.23E-03 MAX ERROR = 6.16E-03 AT OBS.NO. 7
RESIDUALS SQUARED = 1.46E-04
RFACTOR = 0.0285 PERCENT

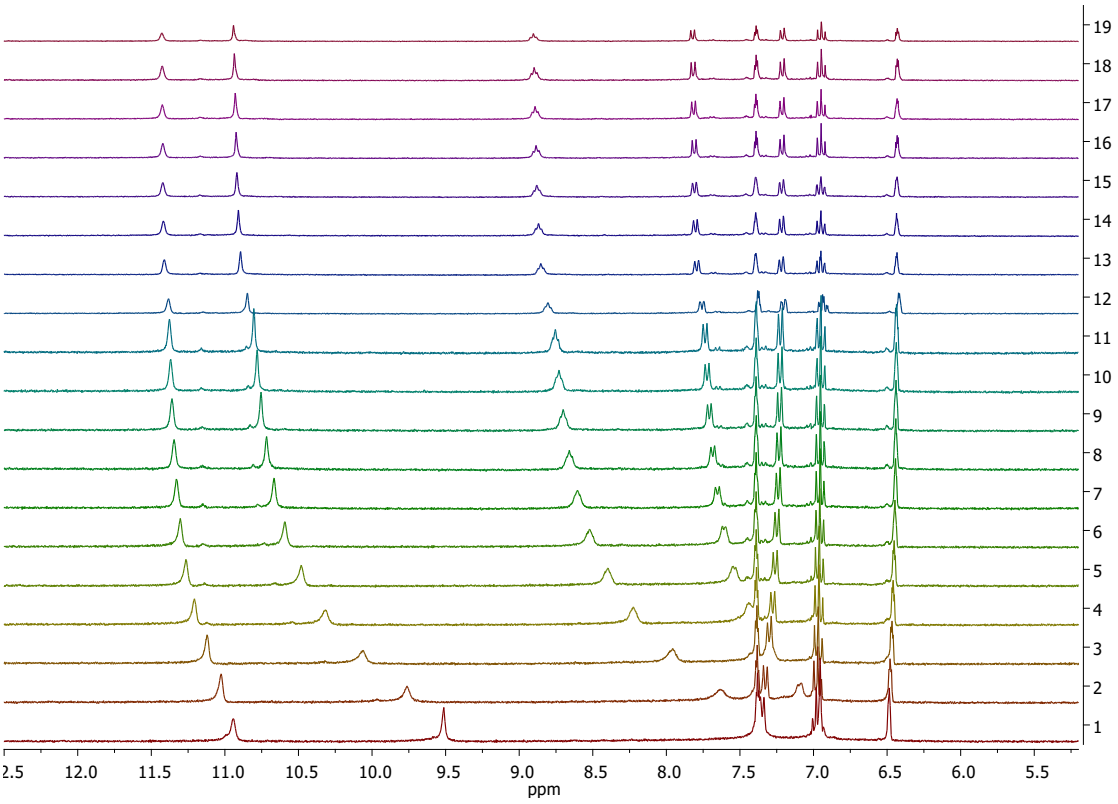


Figure S43. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.2 M solution of TBACl, prepared with a 0.01 M solution of **L2**, to a 0.01 M solution of **L2**.

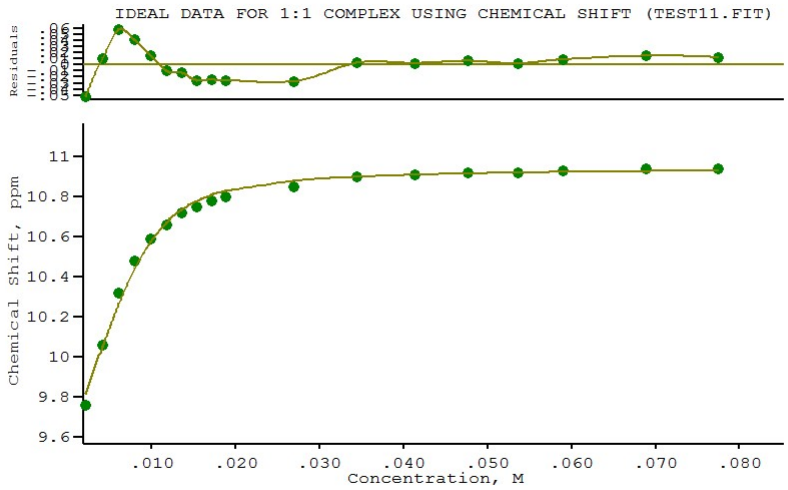


Figure S44. Fitted binding isotherm obtained for the titration of a 0.01 M solution of compound **L2** with a 0.2 M solution of TBACl (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 1083 ± 143 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 12:28:00 on 01/15/2018

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes. October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	1.08279E+03	2.000E-01	1.433E+02	3.586E+00	K1
2	1	9.55626E+00	2.000E-01	2.702E-02	1.547E+00	SHIFT Sn
3	1	1.09455E+01	1.000E+00	1.307E-02	2.816E+00	SHIFT Sn(L)

0RMS ERROR = 2.78E-02 MAX ERROR = 5.82E-02 AT OBS.NO. 3
RESIDUALS SQUARED = 1.16E-02
RFACTOR = 0.2372 PERCENT

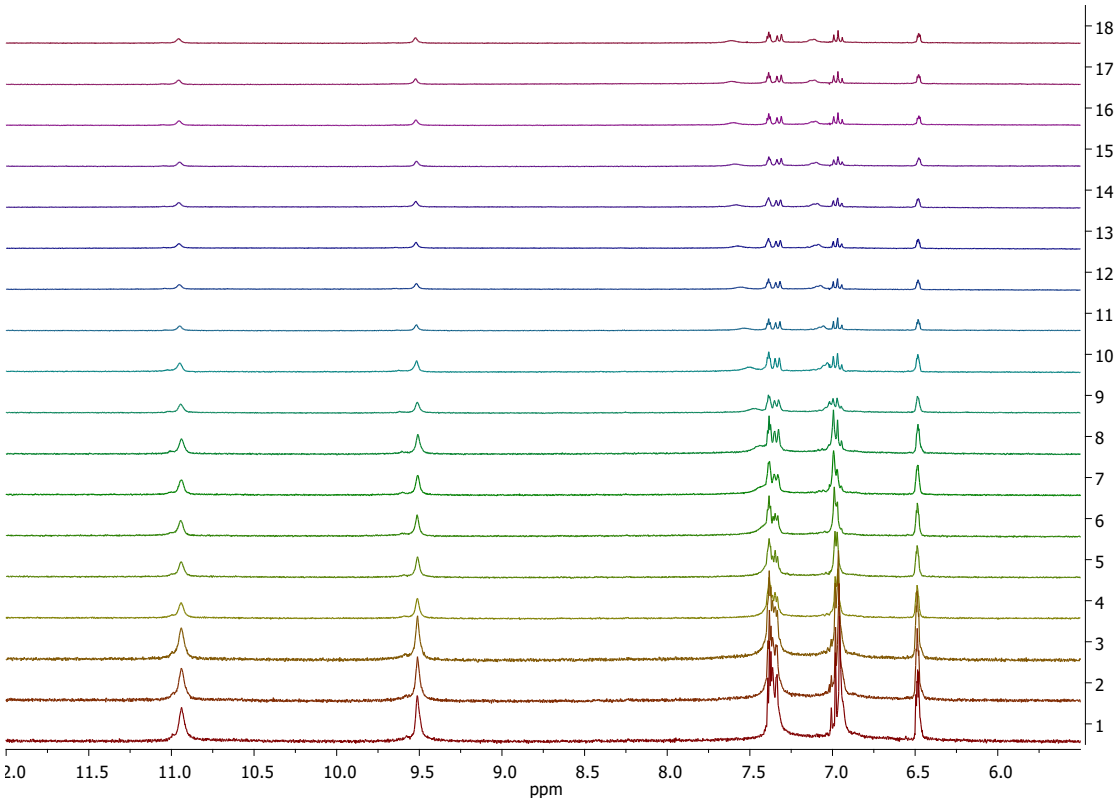


Figure S45. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.6 M solution of $TBANO_3$, prepared with a 0.01 M solution of **L2**, to a 0.01 M solution of **L2**.

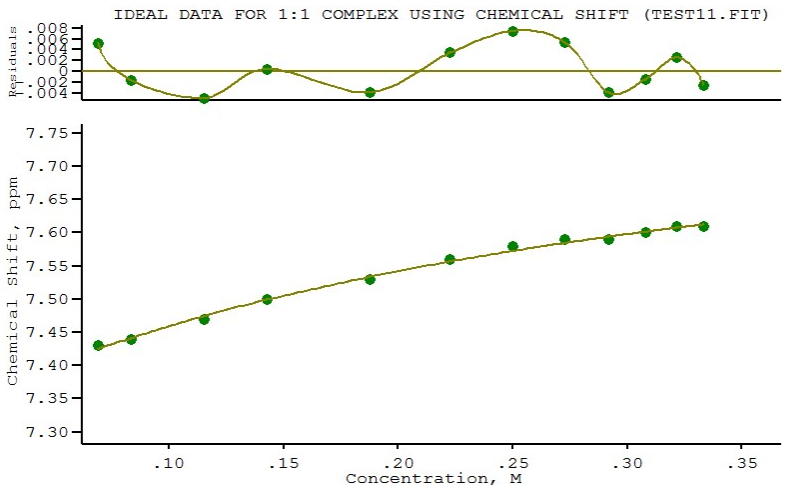


Figure S46. Fitted binding isotherm obtained for the titration of a 0.01 M solution of compound **L2** with a 0.6 M solution of $TBANO_3$ (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 3.4 ± 0.9 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 18:26:18 on 02/15/2018

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes. October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	3.37863E+00	2.000E-01	8.703E-01	4.767E+02	K1
2	1	7.32260E+00	2.000E-01	1.682E-02	5.598E+01	SHIFT Sn
3	1	7.87245E+00	1.000E+00	4.748E-02	2.359E+02	SHIFT Sn(L)

0RMS ERROR = 4.64E-03 MAX ERROR = 7.48E-03 AT OBS.NO. 7
RESIDUALS SQUARED = 1.94E-04
RFACTOR = 0.0532 PERCENT

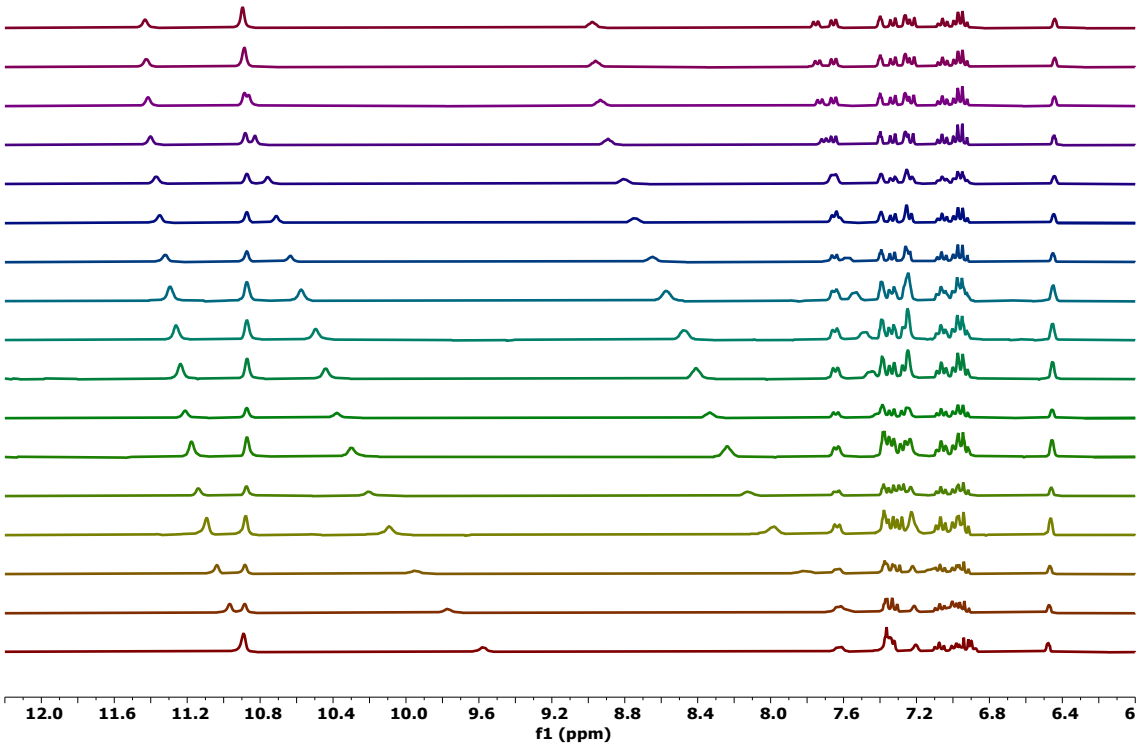


Figure S47. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of TBACl, prepared with a 0.005 M solution of **L3**, to a 0.005 M solution of **L3**.

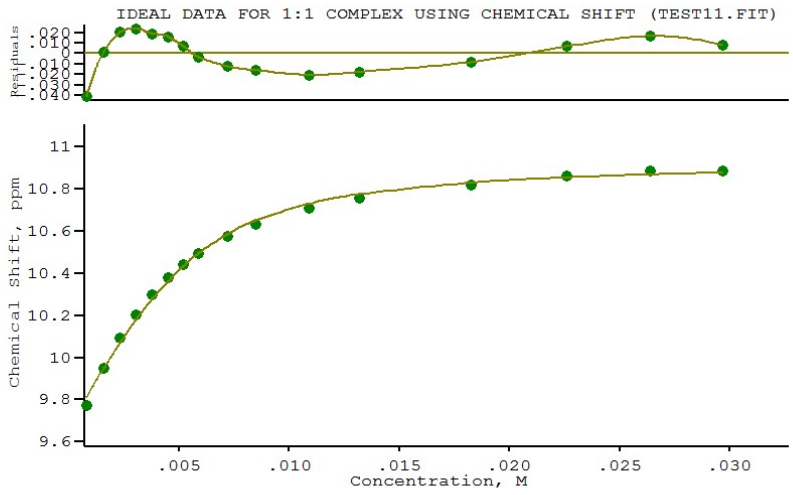


Figure S48. Fitted binding isotherm obtained for the titration of a 0.005 M solution of compound **L3** with a 0.075 M solution of TBACl (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 792 ± 75 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 16:14:00 on 05/20/2022

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes, October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	7.92469E+02	2.000E-01	7.462E+01	6.876E+00	K1
2	1	9.66730E+00	2.000E-01	1.582E-02	2.082E+00	SHIFT Sn
3	1	1.09398E+01	1.000E+00	1.555E-02	4.891E+00	SHIFT Sn(L)

0RMS ERROR = 1.95E-02 MAX ERROR = 4.09E-02 AT OBS.NO. 1
RESIDUALS SQUARED = 4.95E-03
RFACTOR = 0.1676 PERCENT

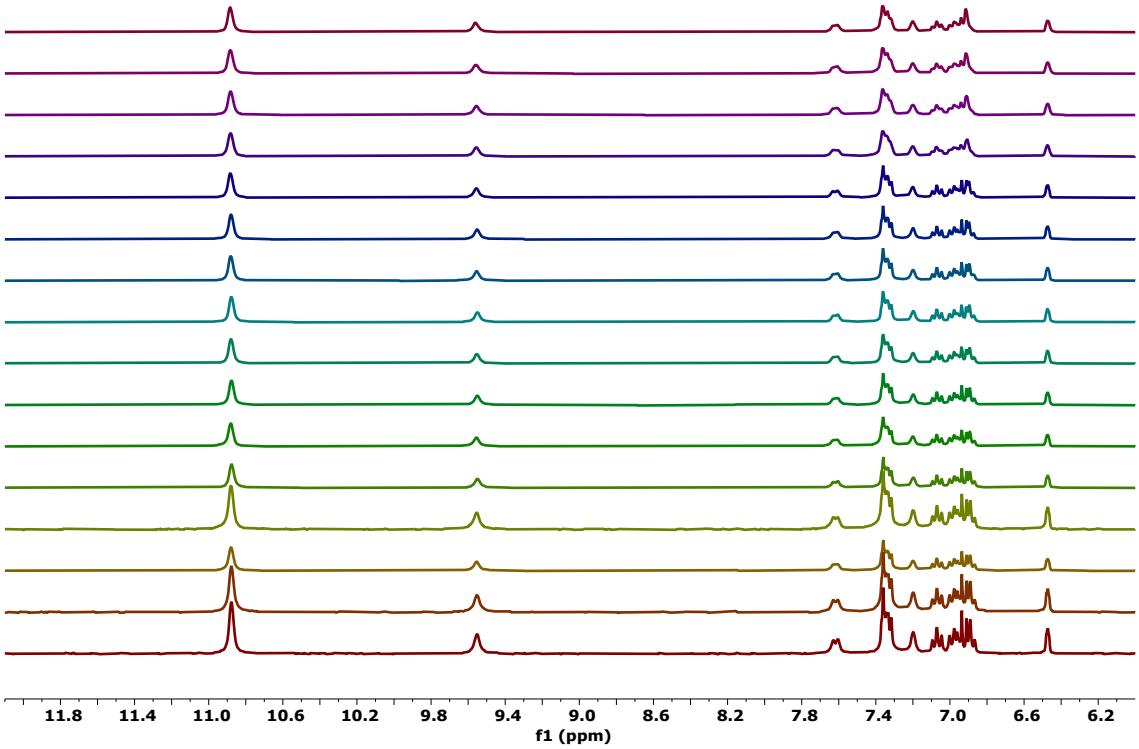


Figure S49. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of $TBANO_3$, prepared with a 0.005 M solution of **L3**, to a 0.005 M solution of **L3**. No binding was observed.

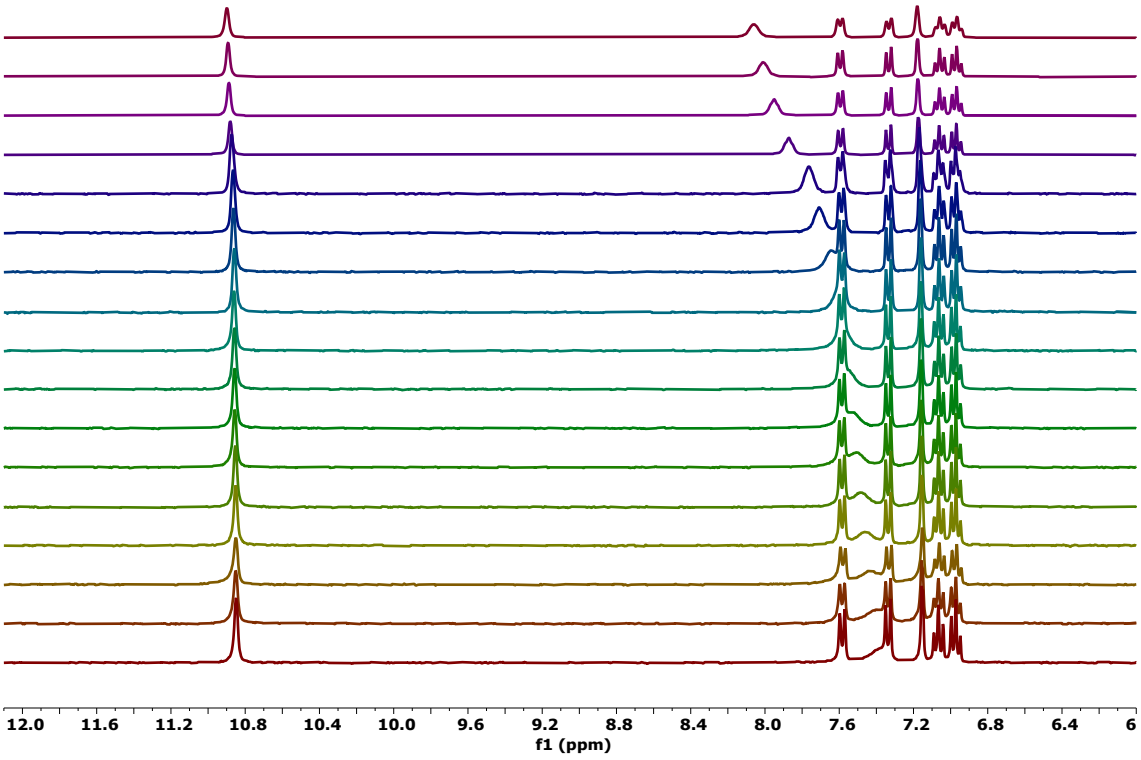


Figure S50. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of TBACl, prepared with a 0.005 M solution of **L4**, to a 0.005 M solution of **L4**.

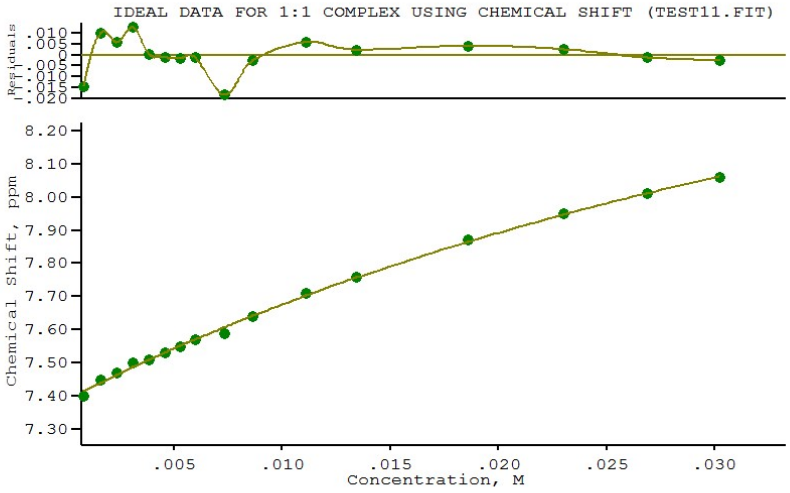


Figure S51. Fitted binding isotherm obtained for the titration of a 0.005 M solution of compound **L4** with a 0.075 M solution of TBACl (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 19 ± 3 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 15:22:02 on 05/20/2022

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes, October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	1.93728E+01	2.000E-01	2.613E+00	2.221E+02	K1
2	1	7.38808E+00	2.000E-01	5.574E-03	5.208E+00	SHIFT Sn
3	1	9.28065E+00	1.000E+00	1.587E-01	1.855E+02	SHIFT Sn(L)

0RMS ERROR = 8.42E-03 MAX ERROR = 1.82E-02 AT OBS.NO. 9
RESIDUALS SQUARED = 9.22E-04
RFACTOR = 0.0991 PERCENT

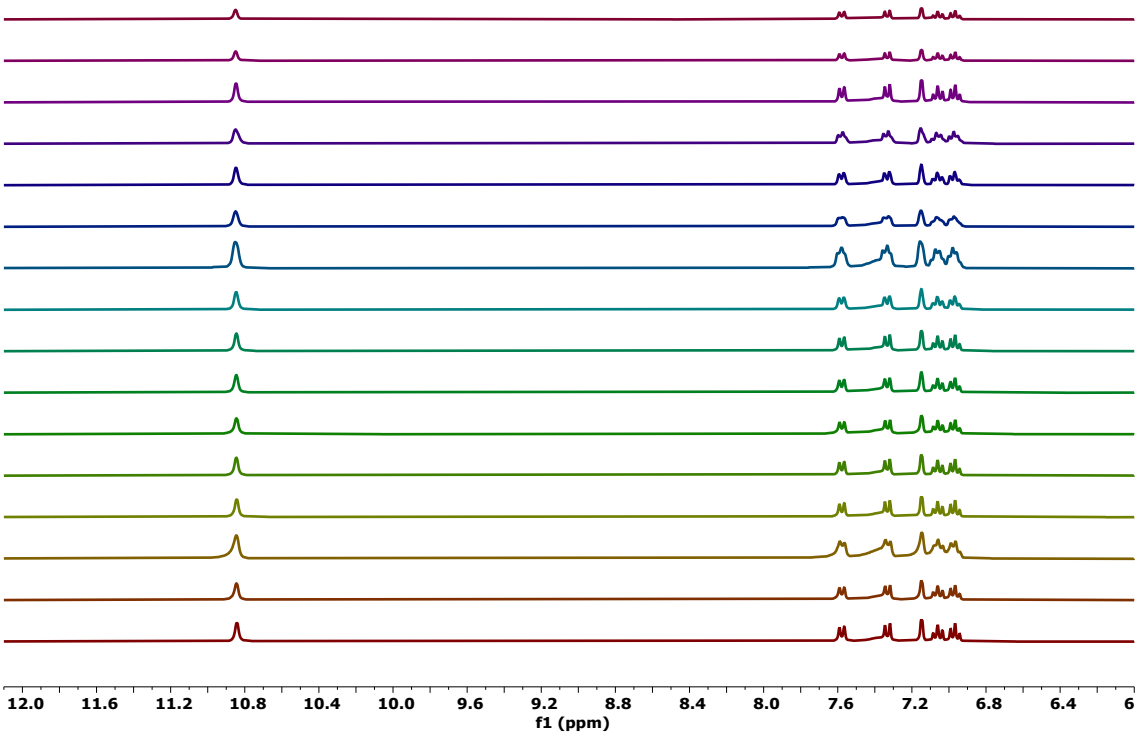


Figure S52. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of $TBANO_3$, prepared with a 0.005 M solution of **L4**, to a 0.005 M solution of **L4**. No binding was observed.

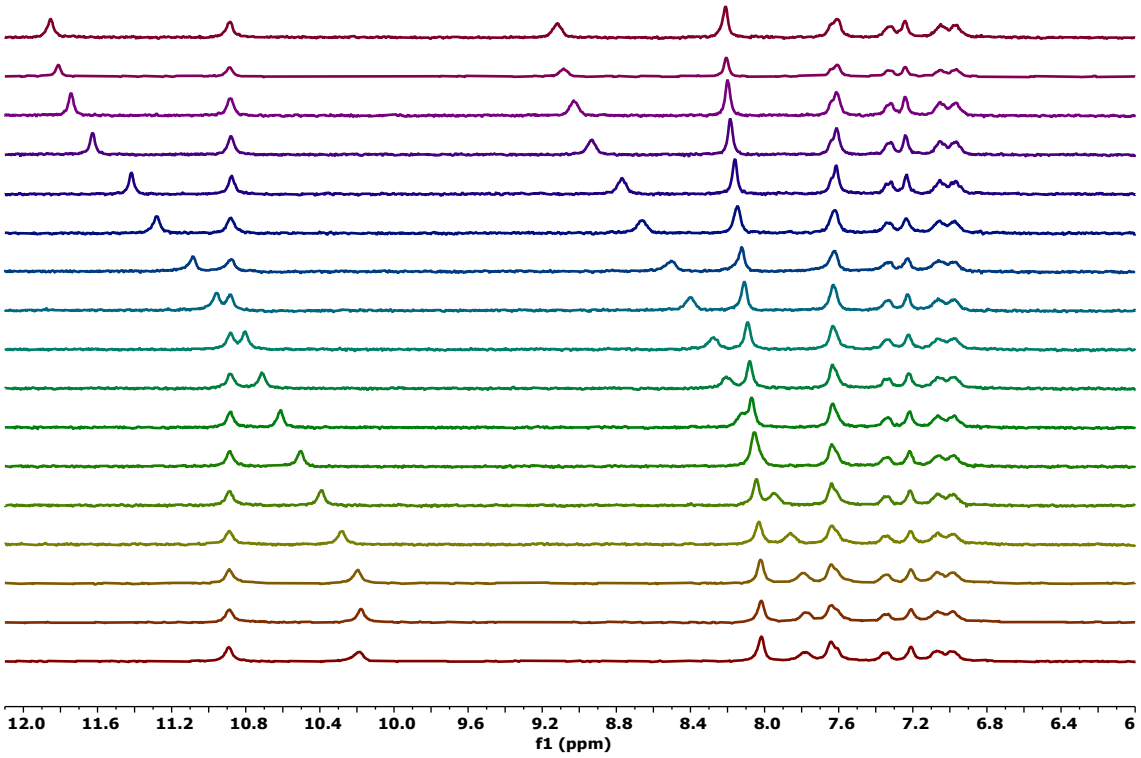


Figure S53. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of TBACl, prepared with a 0.005 M solution of **L5**, to a 0.005 M solution of **L5**.

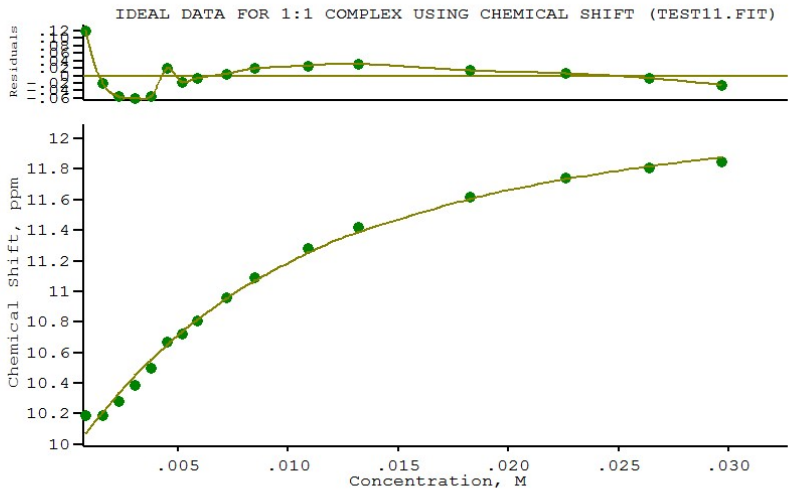


Figure S54. Fitted binding isotherm obtained for the titration of a 0.005 M solution of compound **L5** with a 0.075 M solution of TBACl (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 143 ± 17 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 15:51:50 on 05/20/2022

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes, October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	1.43004E+02	2.000E-01	1.713E+01	1.707E+01	K1
2	1	9.91769E+00	2.000E-01	3.541E-02	3.590E+00	SHIFT Sn
3	1	1.24107E+01	1.000E+00	7.893E-02	1.062E+01	SHIFT Sn(L)

0RMS ERROR = 4.65E-02 MAX ERROR = 1.20E-01 AT OBS.NO. 1
RESIDUALS SQUARED = 2.81E-02
RFACTOR = 0.3814 PERCENT

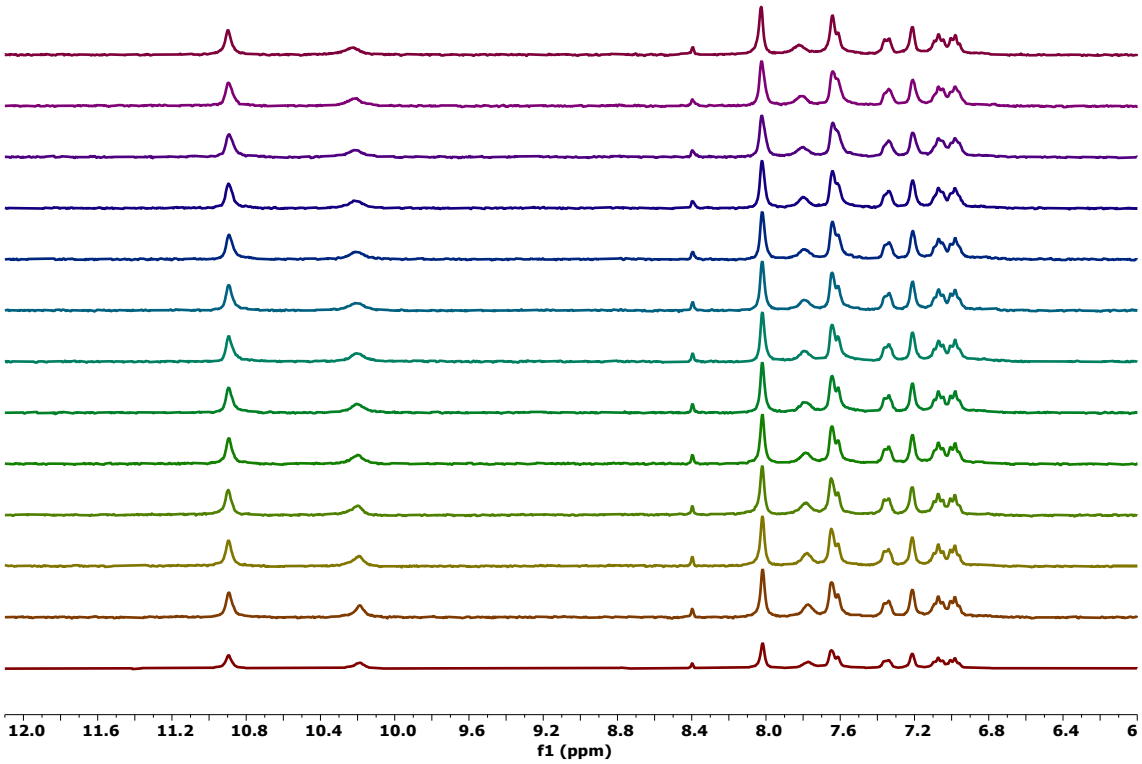


Figure S55. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of $TBANO_3$, prepared with a 0.005 M solution of **L5**, to a 0.005 M solution of **L5**. No binding was observed.

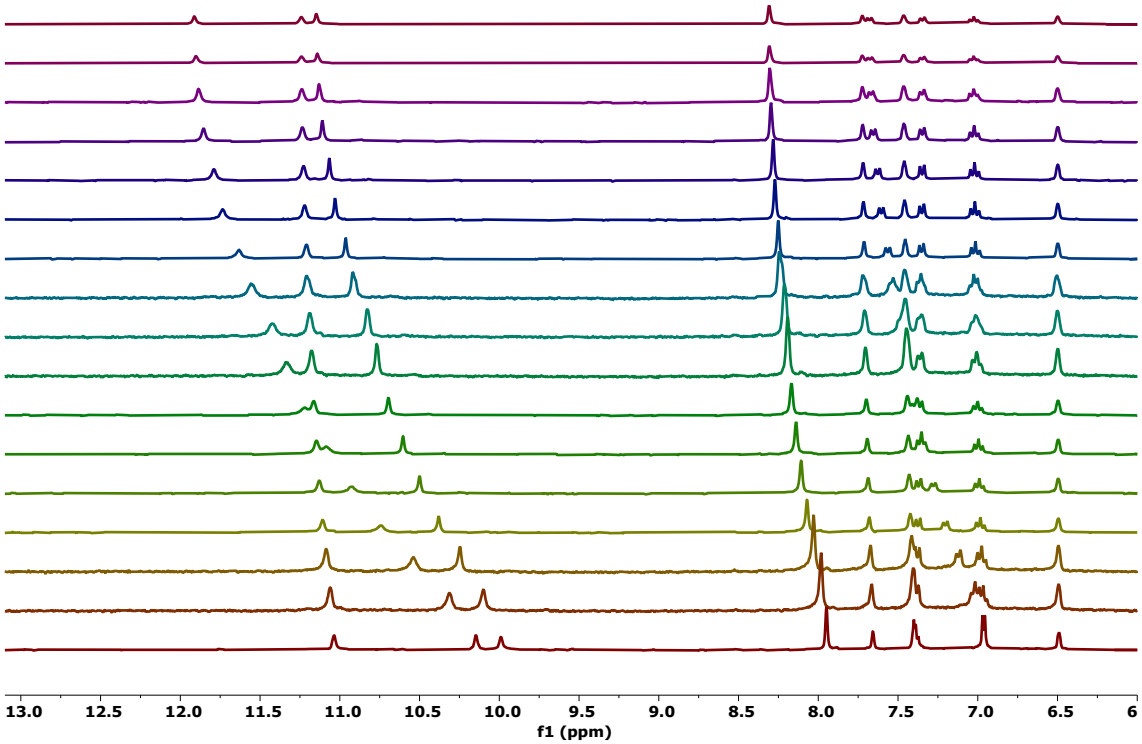


Figure S56. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of TBACl, prepared with a 0.005 M solution of **L6**, to a 0.005 M solution of **L6**.

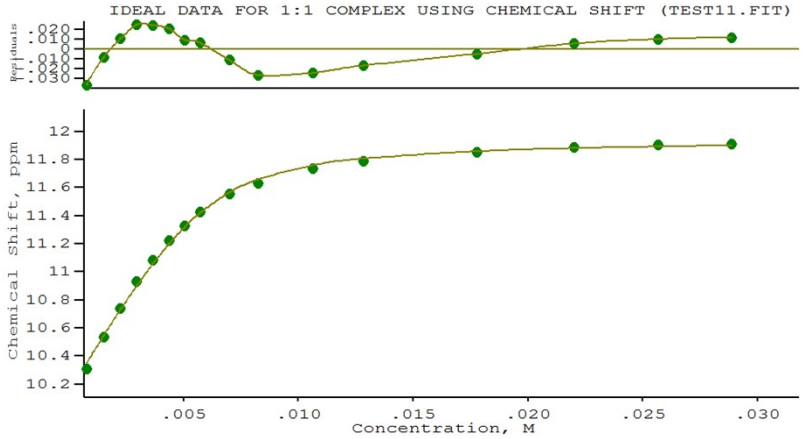


Figure S57. Fitted binding isotherm obtained for the titration of a 0.005 M solution of compound **L6** with a 0.075 M solution of TBACl (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 1619 ± 136 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 12:44:16 on 05/20/2022

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes, October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	1.61933E+03	2.000E-01	1.362E+02	4.884E+00	K1
2	1	1.01395E+01	2.000E-01	1.490E-02	1.571E+00	SHIFT Sn
3	1	1.19449E+01	1.000E+00	1.374E-02	3.999E+00	SHIFT Sn(L)

0RMS ERROR = 2.01E-02 MAX ERROR = 3.62E-02 AT OBS.NO. 1
RESIDUALS SQUARED = 5.28E-03
RFACTOR = 0.1597 PERCENT

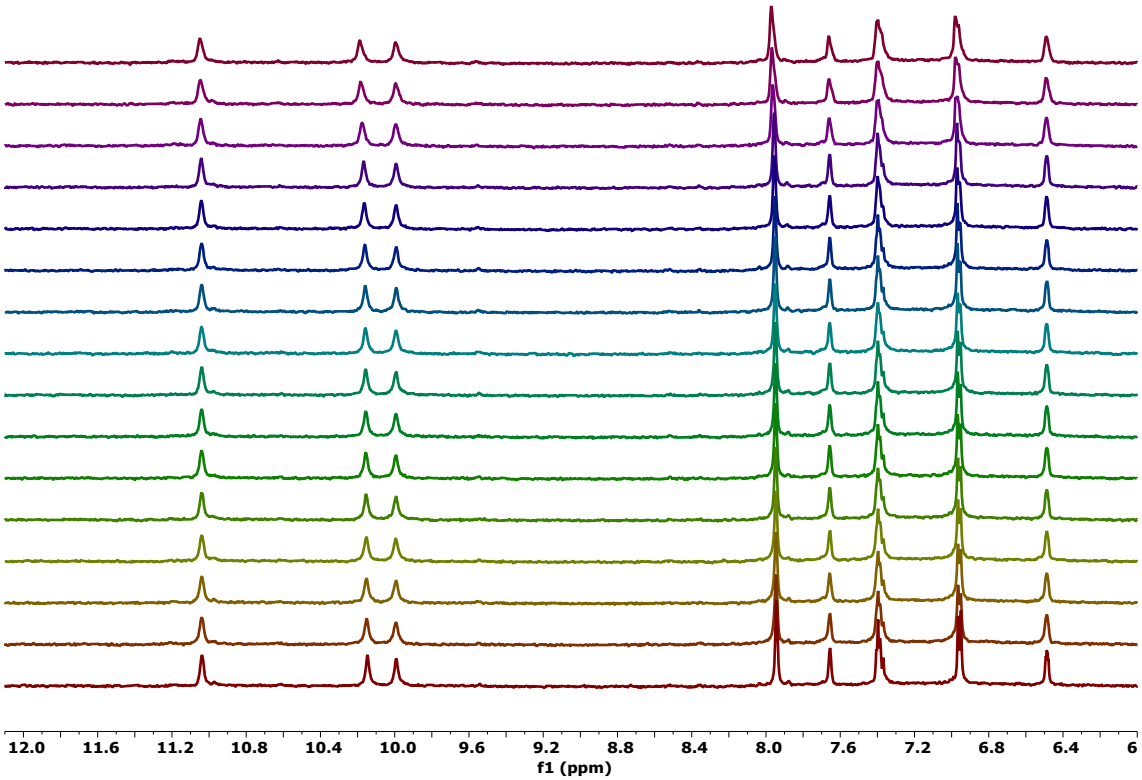


Figure S58. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of $TBANO_3$, prepared with a 0.005 M solution of **L6**, to a 0.005 M solution of **L6**. No binding was observed.

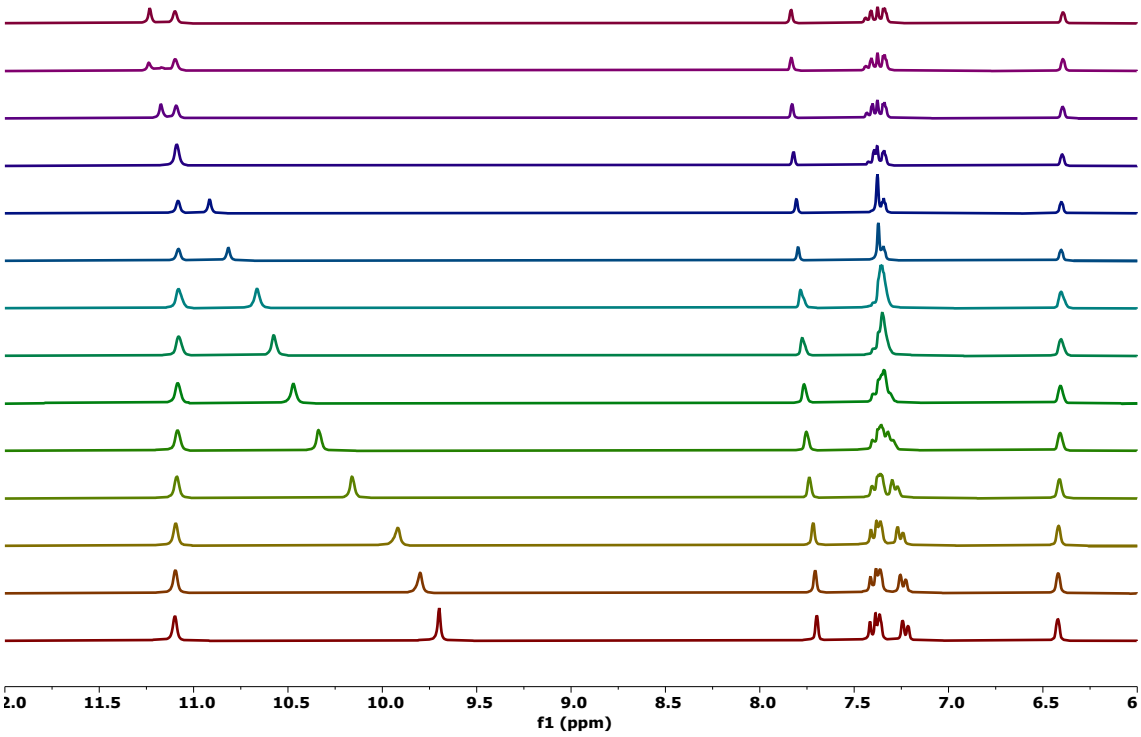


Figure S59. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of TBACl, prepared with a 0.005 M solution of **L7**, to a 0.005 M solution of **L7**.

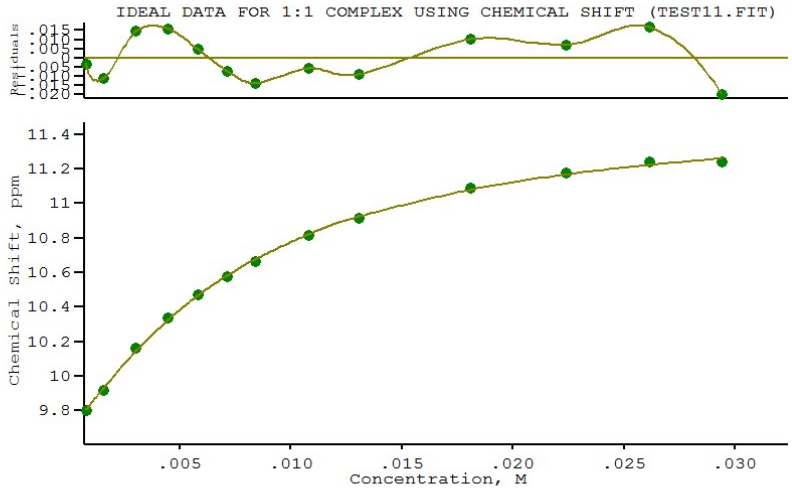


Figure S60. Fitted binding isotherm obtained for the titration of a 0.005 M solution of compound **L7** with a 0.075 M solution of TBACl (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 201 ± 10 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 16:01:06 on 05/20/2022

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes, October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	2.01300E+02	2.000E-01	1.043E+01	1.776E+01	K1
2	1	9.66320E+00	2.000E-01	1.195E-02	3.066E+00	SHIFT Sn
3	1	1.15736E+01	1.000E+00	2.272E-02	1.208E+01	SHIFT Sn(L)

0RMS ERROR = 1.34E-02 MAX ERROR = 2.01E-02 AT OBS.NO. 13
RESIDUALS SQUARED = 1.80E-03
RFACTOR = 0.1105 PERCENT

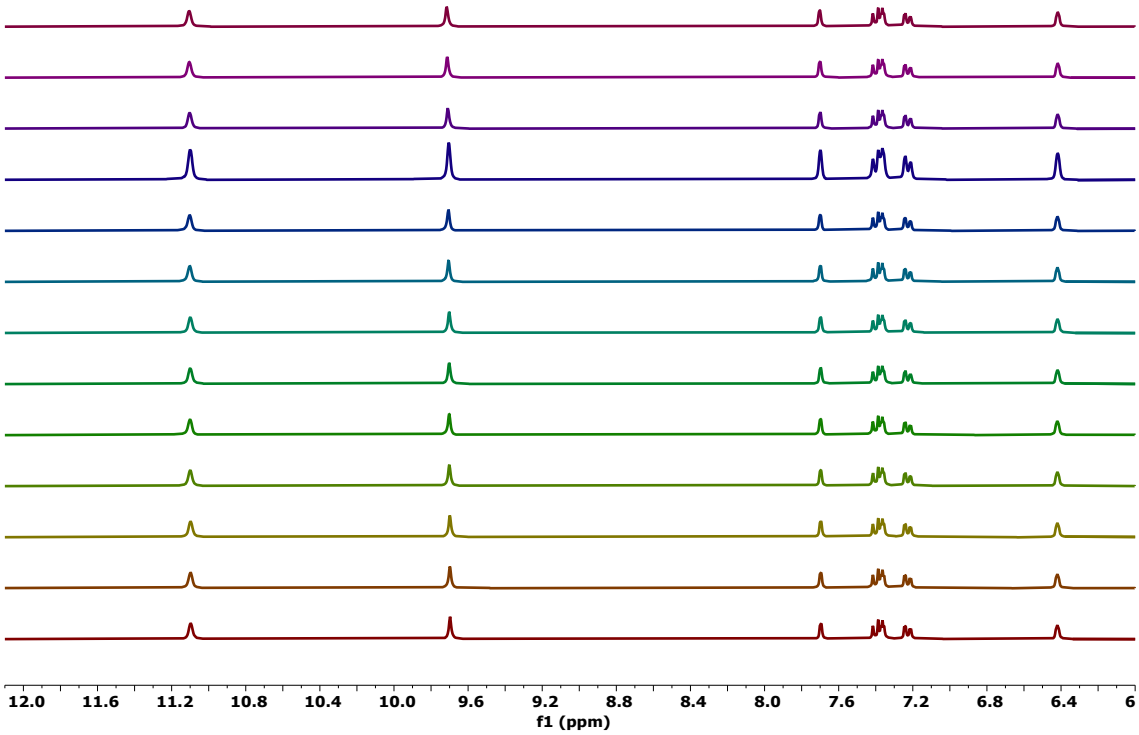


Figure S61. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of $TBANO_3$, prepared with a 0.005 M solution of **L7**, to a 0.005 M solution of **L7**. No binding was observed.

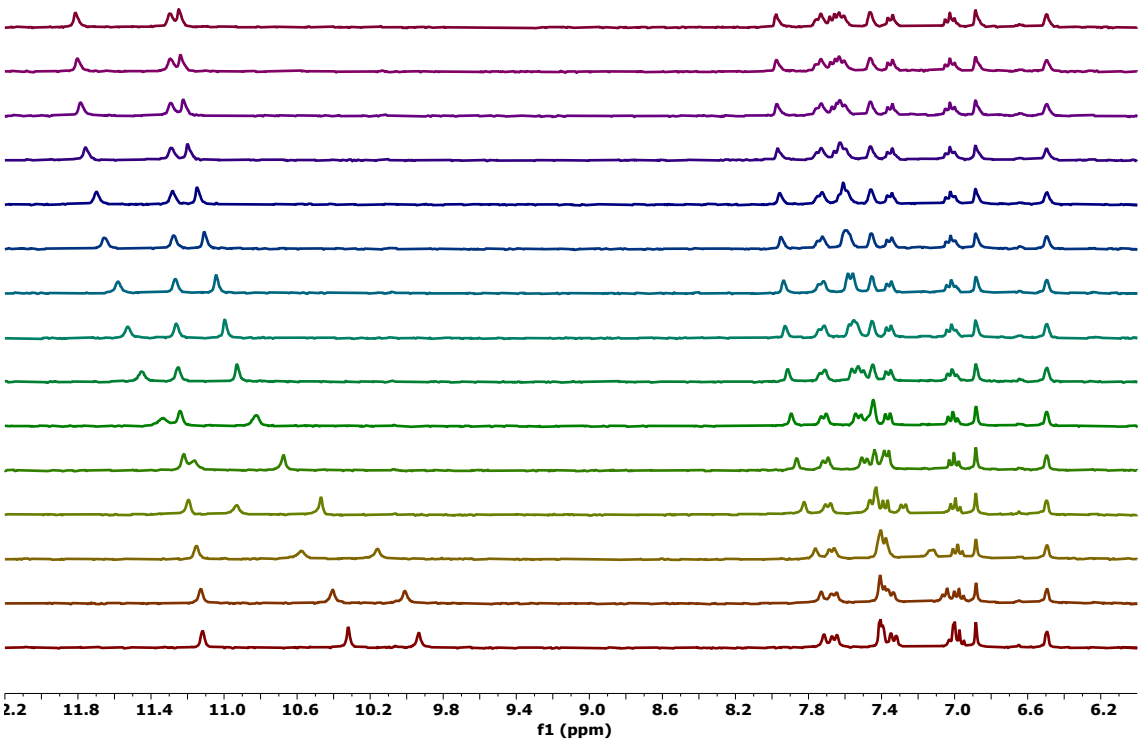


Figure S62. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of TBACl, prepared with a 0.005 M solution of **L8**, to a 0.005 M solution of **L8**.

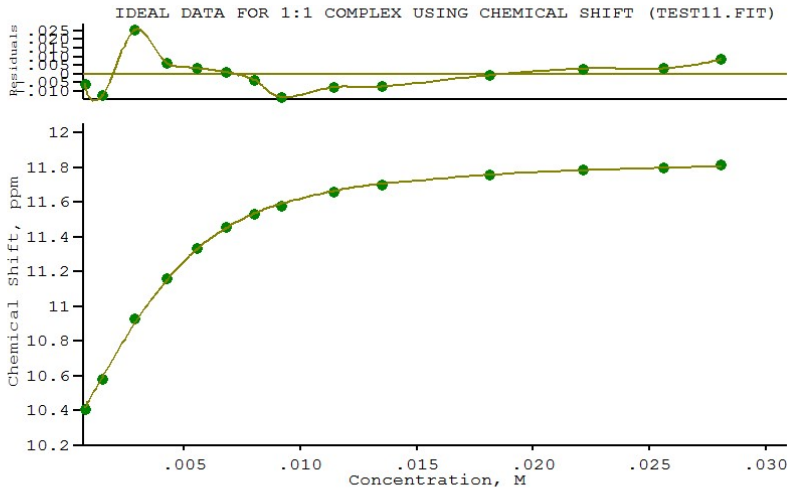


Figure S63. Fitted binding isotherm obtained for the titration of a 0.005 M solution of compound **L8** with a 0.075 M solution of TBACl (DMSO-d_6/0.5% water). In order to avoid the dilution effect the latter was prepared with the former. The graph shows the change in chemical shift of the proton's signal of one of the NH groups of the molecule, fitted to the 1:1 (L:A) binding model. K_a = 1012 ± 44 M^{-1}.

Calculations by WinEQNMR2 Version 2.00 by Michael J. Hynes
Program run at 15:56:20 on 05/20/2022

IDEAL DATA FOR 1:1 COMPLEX USING CHEMICAL SHIFT (TEST11.FIT)
Reaction: Sn + L = Sn(L)
FILE: TEST11.FIT (Measured shift is on 119Sn)
IDEAL DATA: K1 = 63.091; DELTA M = 20.0; DELTA ML = 120.0
File prepared by M. J. Hynes, October 22 2000

Equilibrium constants are floating point numbers

NO.	A	PARAMETER	DELTA	ERROR	CONDITION	DESCRIPTION
1	1	1.01209E+03	2.000E-01	4.441E+01	5.663E+00	K1
2	1	1.02195E+01	2.000E-01	9.392E-03	1.646E+00	SHIFT Sn
3	1	1.18724E+01	1.000E+00	8.106E-03	4.503E+00	SHIFT Sn(L)

0RMS ERROR = 1.08E-02 MAX ERROR = 2.55E-02 AT OBS.NO. 3
RESIDUALS SQUARED = 1.29E-03
RFACTOR = 0.0843 PERCENT

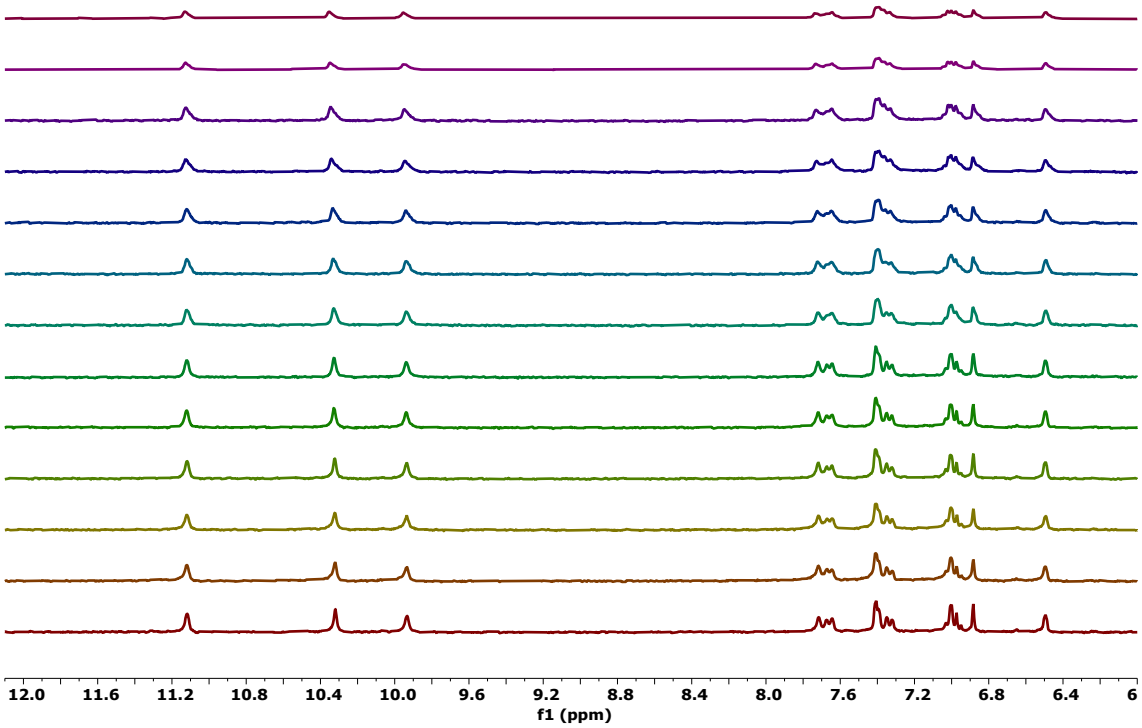


Figure S64. Excerpt of the ^{1}H NMR spectra (300 MHz, DMSO-d_6/0.5% water, 298 K) obtained upon addition of different aliquots of a 0.075 M solution of $TBANO_3$, prepared with a 0.005 M solution of **L8**, to a 0.005 M solution of **L8**. No binding was observed.

5. TRANSMEMBRANE ANION TRANSPORT EXPERIMENTS IN VESICLES[10]

5.1. Preparation of phospholipid vesicles

A chloroform solution of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocoline (POPC) (20 mg/mL) (Sigma Aldrich) (or a 7:3 POPC:cholesterol mixture, in the case of HPTS-based assays) was evaporated under reduced pressure using a rotary evaporator and the resulting film was dried under high vacuum for at least 8 h. Different aqueous solutions were used to rehydrate the lipid film: (a) ISE assays: 489 mM NaCl, 5 mM NaH_2PO_4, Ionic Strength (I.S.) 500 mM, pH 7.2, for Cl^-/NO_3^- exchange experiments, or 451 mM NaCl, 20 mM NaH_2PO_4, I.S. 500 mM, pH 7.2, for Cl^-/HCO_3^- exchange experiments; (b) Carboxyfluorescein-based assays: 451 mM NaCl, 20 mM NaH_2PO_4, 50 mM CF, I.S. 500 mM, pH 7.2; (c) HPTS-based assays: 126.2 mM $NaNO_3$, 10 mM NaH_2PO_4, 1 mM HPTS, pH 7.2. The resulting suspension was vortexed and subjected to nine freeze-thaw cycles; subsequently, it was extruded twenty-nine times through a polycarbonate membrane (200 nm) employing a LiposoFast basic extruder (Avestin, Inc.). The resulting unilamellar vesicles were: (a) ISE assays: dialysed against a $NaNO_3$ aqueous solution (489 mM $NaNO_3$, 5 mM NaH_2PO_4, I.S. 500 mM, pH 7.2, for Cl^-/NO_3^- exchange experiments) or a Na_2SO_4 aqueous solution (150 mM Na_2SO_4, 20 mM NaH_2PO_4, I.S. 500 mM, pH 7.2, for Cl^-/HCO_3^- exchange experiments) to remove the unencapsulated chloride; (b) Carboxyfluorescein-based assays: subjected to size-exclusion chromatography, using Sephadex G-25 as the stationary phase and a Na_2SO_4 aqueous solution (150 mM Na_2SO_4, 20 mM NaH_2PO_4, I.S. 500 mM, pH 7.2) as the mobile phase, to remove the unencapsulated carboxyfluorescein; (c) HPTS-based assays: subjected to size-exclusion chromatography, using Sephadex G-25 as the stationary phase and the inner solution without HPTS (126.2 mM $NaNO_3$, 10 mM NaH_2PO_4, pH 7.2) as the mobile phase, to remove the unencapsulated HPTS. Vesicles were collected in a 10-mL volumetric flask, using either the external solution (ISE and carboxyfluorescein-based assays) or the inner one without the probe (HPTS-based assays) to bring the suspension to the desired volume.

5.2. ISE transport experiments

Unilamellar vesicles (mean diameter: 200 nm) made of POPC and containing a NaCl aqueous solution (489 mM NaCl, 5 mM NaH_2PO_4, I.S. 500 mM, pH 7.2, for Cl^-/NO_3^- exchange experiments, or 451 mM NaCl, 20 mM NaH_2PO_4, I.S. 500 mM, pH 7.2, for Cl^-/HCO_3^- exchange experiments) were dispersed in a $NaNO_3$ aqueous solution (489 mM $NaNO_3$, 5 mM NaH_2PO_4, I.S. 500 mM, pH 7.2, for Cl^-/NO_3^- exchange experiments) or a Na_2SO_4 aqueous solution (150 mM

[10] I. Carreira-Barral, M. Mielczarek, D. Alonso-Carrillo, V. Capurro, V. Soto-Cerrato, R. Pérez-Tomás, E. Caci, M. García-Valverde and R. Quesada, *Chem. Commun.*, 2020, **56**, 3218-3221.

Na_2SO_4, 20 mM NaH_2PO_4, I.S. 500 mM, pH 7.2, for Cl^-/HCO_3^- exchange experiments), the final lipid concentration during the assays being 0.5 mM and the final volume 5 mL. A certain volume of a solution of the corresponding compound in DMSO (or the blank, DMSO, 12.5 µL) was added at t = 0 s, and the chloride released was monitored for 300 s with a Fisherbrand™ Accumet™ chloride combination electrode. At t = 300 s a surfactant (Triton-X, 20% dispersion in water, 20 µL) was added to lyse the vesicles and free all the encapsulated chloride. This value was considered as 100% release and employed as such. Regarding the Cl^-/HCO_3^- exchange assays, a 500 mM $NaHCO_3$ aqueous solution prepared with the Na_2SO_4 one (150 mM Na_2SO_4, 20 mM NaH_2PO_4, I.S. 500 mM, pH 7.2) was added at t = -10 s to the vesicles suspension, the HCO_3^- concentration during the assay being 40 mM. The rest of the experimental procedure is similar to that described previously.

Cl^-/NO_3^- exchange assays

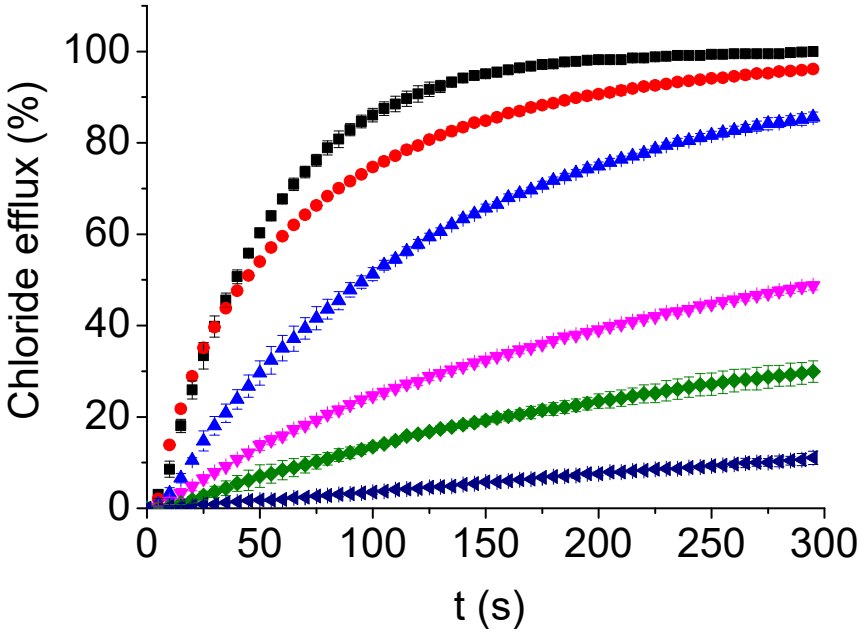


Figure S65. Chloride efflux promoted by compound **L1** (5 µM, black; 2.5 µM, red; 0.5 µM, light blue; 0.15 µM, pink; 0.05 µM, green; 0.025 µM, dark blue) in unilamellar POPC vesicles. Vesicles were loaded with a 489 mM NaCl solution buffered at pH 7.2 with 5 mM NaH_2PO_4 and dispersed in a 489 mM $NaNO_3$ solution buffered at pH 7.2 with 5 mM NaH_2PO_4. Each trace represents the average of at least three trials, performed with three batches of vesicles.

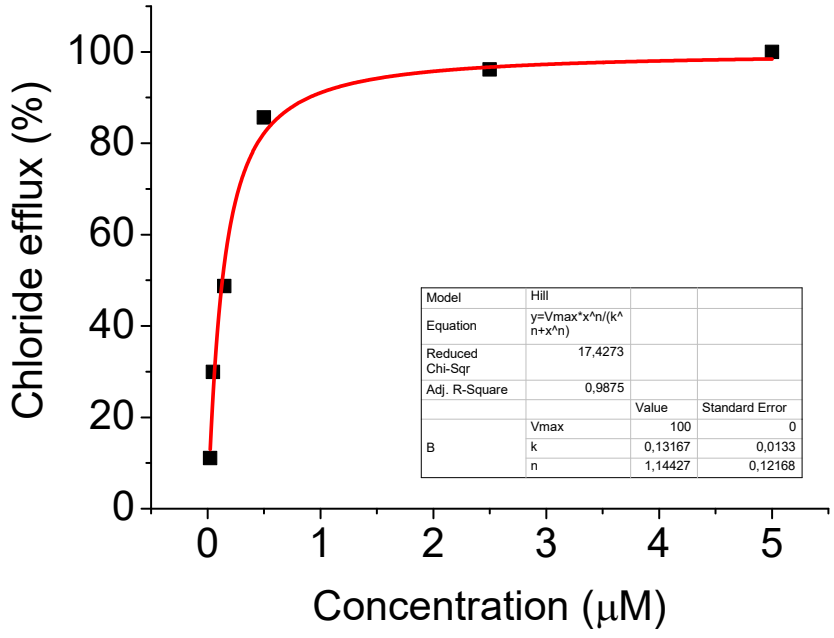


Figure S66. Hill analysis for compound **L1**.

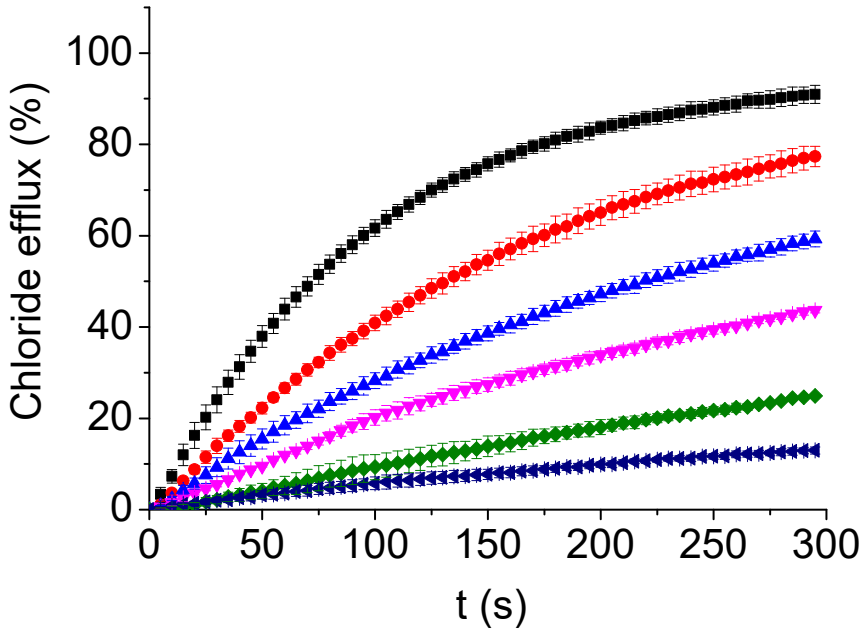


Figure S67. Chloride efflux promoted by compound **L2** (35 µM, black; 25 µM, red; 15 µM, light blue; 10 µM, pink; 5 µM, green; 2.5 µM, dark blue) in unilamellar POPC vesicles. Vesicles were loaded with a 489 mM NaCl solution buffered at pH 7.2 with 5 mM NaH_2PO_4 and dispersed in a 489 mM $NaNO_3$ solution buffered at pH 7.2 with 5 mM NaH_2PO_4. Each trace represents the average of at least three trials, performed with at least three batches of vesicles.

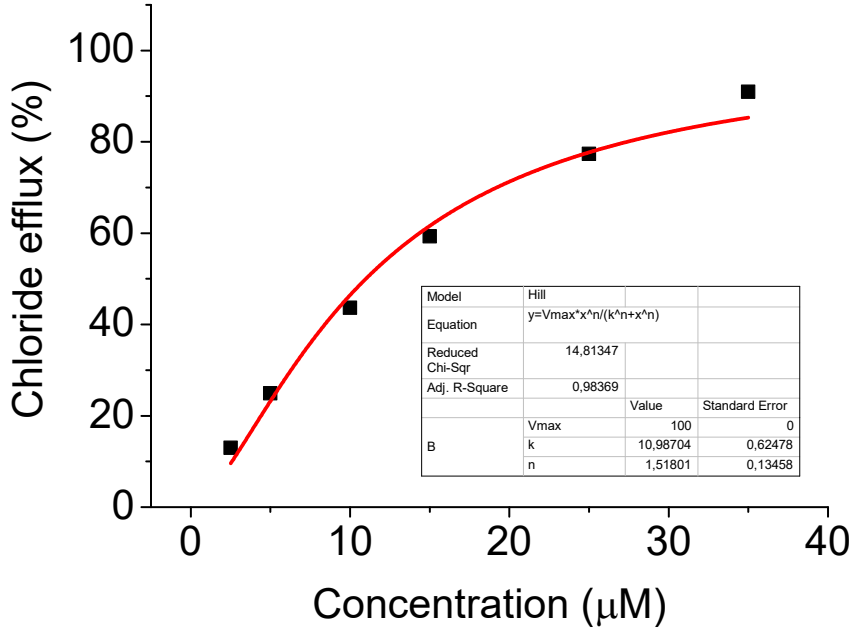


Figure S68. Hill analysis for compound **L2**.

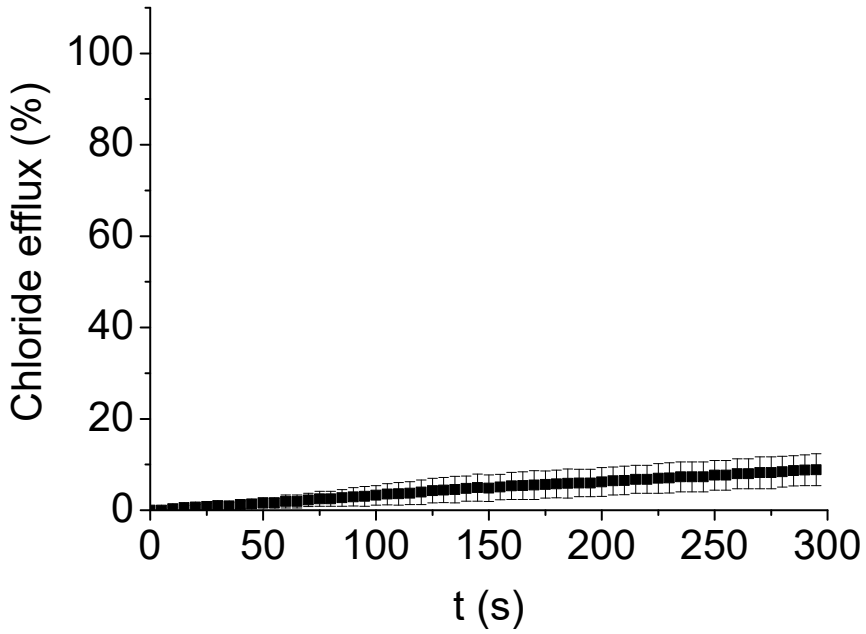


Figure S69. Chloride efflux promoted by compound **L3** (5 μM, black) in unilamellar POPC vesicles. Vesicles were loaded with a 489 mM NaCl solution buffered at pH 7.2 with 5 mM NaH_2PO_4 and dispersed in a 489 mM $NaNO_3$ solution buffered at pH 7.2 with 5 mM NaH_2PO_4. The trace represents the average of three trials, performed with three batches of vesicles.

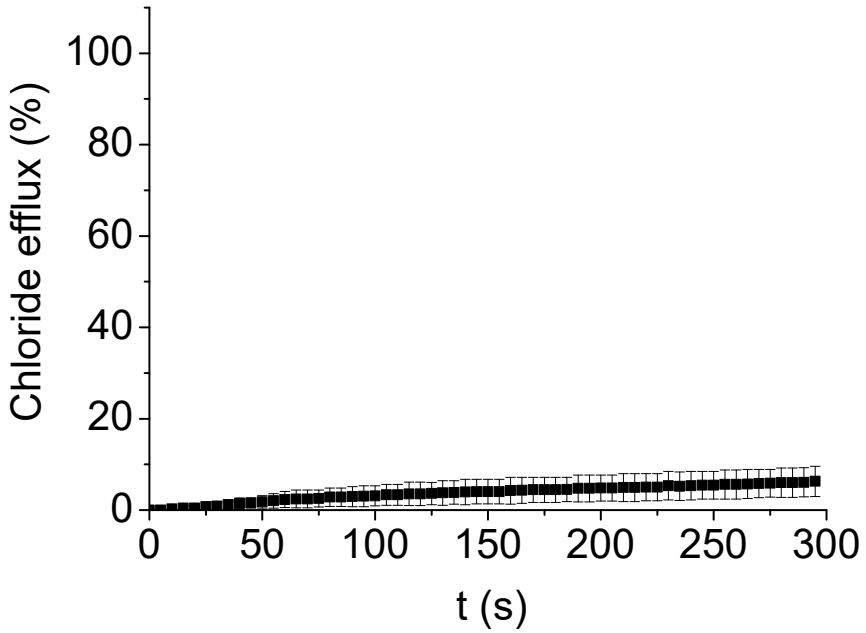


Figure S70. Chloride efflux promoted by compound **L4** (5 μM, black) in unilamellar POPC vesicles. Vesicles were loaded with a 489 mM NaCl solution buffered at pH 7.2 with 5 mM NaH_2PO_4 and dispersed in a 489 mM $NaNO_3$ solution buffered at pH 7.2 with 5 mM NaH_2PO_4. The trace represents the average of three trials, performed with three batches of vesicles.

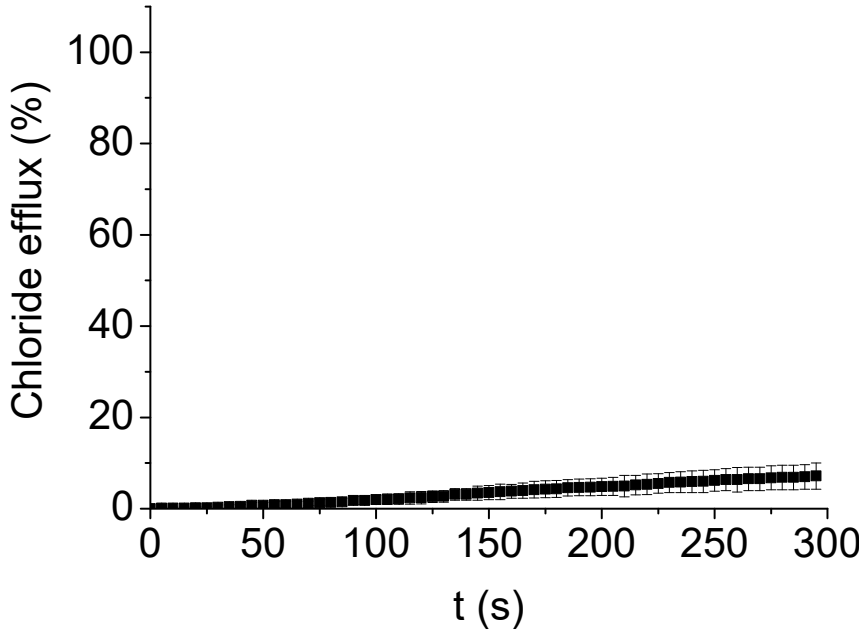


Figure S71. Chloride efflux promoted by compound **L5** (5 µM, black) in unilamellar POPC vesicles. Vesicles were loaded with a 489 mM NaCl solution buffered at pH 7.2 with 5 mM NaH_2PO_4 and dispersed in a 489 mM $NaNO_3$ solution buffered at pH 7.2 with 5 mM NaH_2PO_4. The trace represents the average of three trials, performed with three batches of vesicles.

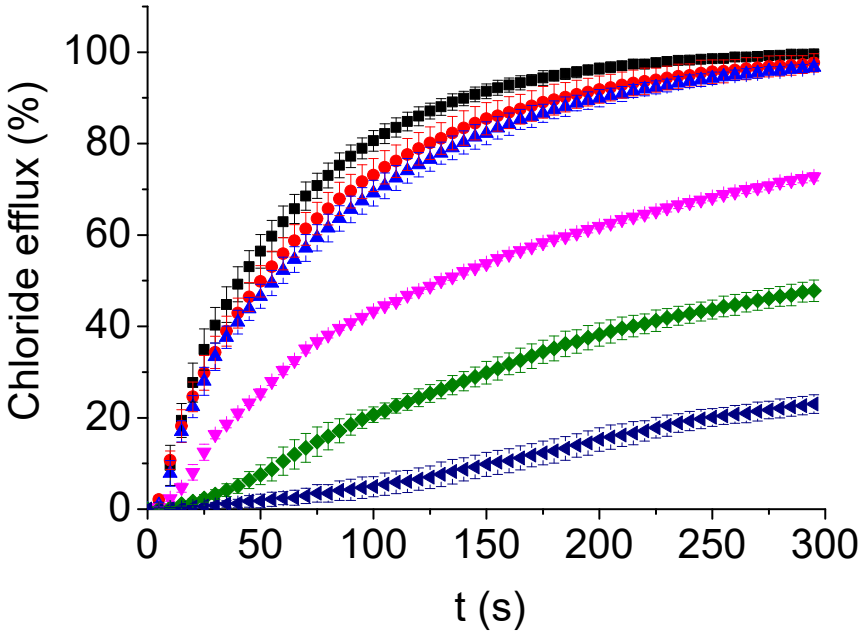


Figure S72. Chloride efflux promoted by compound **L6** (5 µM, black; 2.5 µM, red; 1.5 µM, light blue; 0.15 µM, pink; 0.05 µM, green; 0.025 µM, dark blue) in unilamellar POPC vesicles. Vesicles were loaded with a 489 mM NaCl solution buffered at pH 7.2 with 5 mM NaH_2PO_4 and dispersed in a 489 mM $NaNO_3$ solution buffered at pH 7.2 with 5 mM NaH_2PO_4. Each trace represents the average of at least three trials, performed with three batches of vesicles.

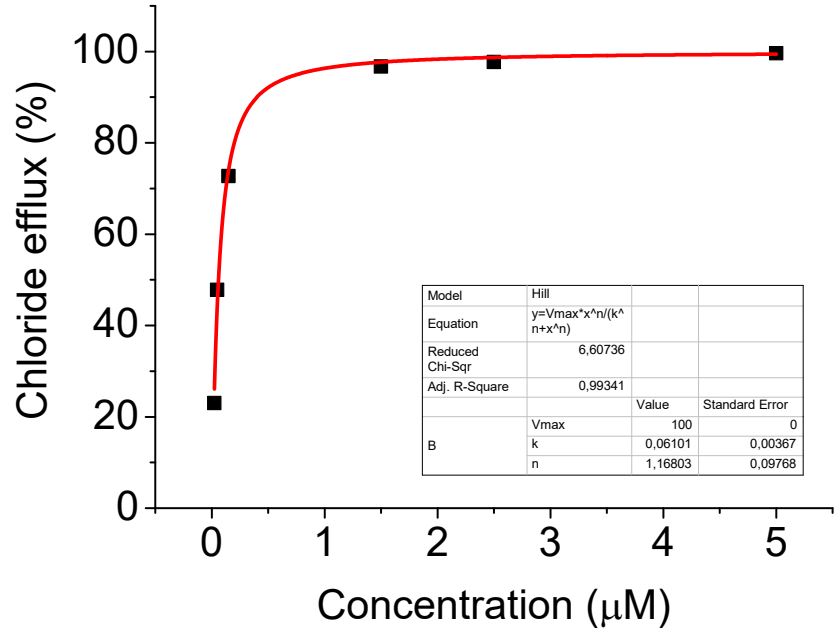


Figure S73. Hill analysis for compound **L6.**

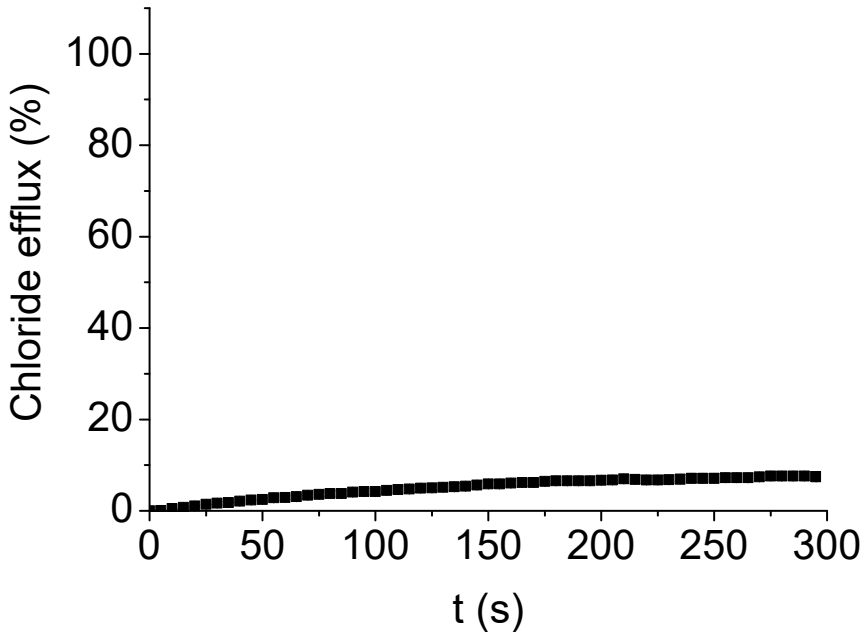


Figure S74. Chloride efflux promoted by compound **L7** (5 μM, black) in unilamellar POPC vesicles. Vesicles were loaded with a 489 mM NaCl solution buffered at pH 7.2 with 5 mM NaH_2PO_4 and dispersed in a 489 mM $NaNO_3$ solution buffered at pH 7.2 with 5 mM NaH_2PO_4. The trace represents the average of three trials, performed with three batches of vesicles.

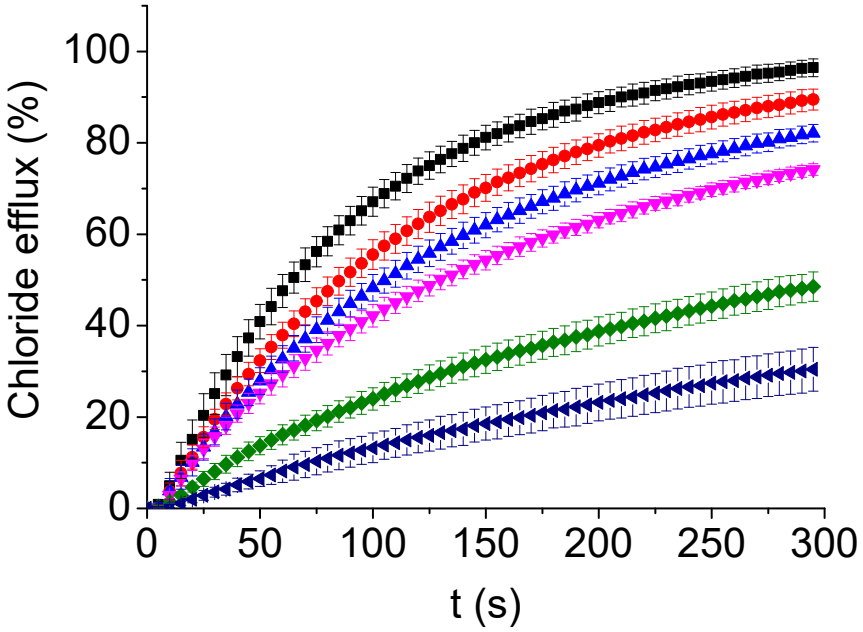


Figure S75. Chloride efflux promoted by compound **L8** (10 μM, black; 5 μM, red; 2.5 μM, light blue; 1.5 μM, pink; 0.5 μM, green; 0.25 μM, dark blue) in unilamellar POPC vesicles. Vesicles were loaded with a 489 mM NaCl solution buffered at pH 7.2 with 5 mM NaH_2PO_4 and dispersed in a 489 mM $NaNO_3$ solution buffered at pH 7.2 with 5 mM NaH_2PO_4. Each trace represents the average of at least three trials, performed with three batches of vesicles.

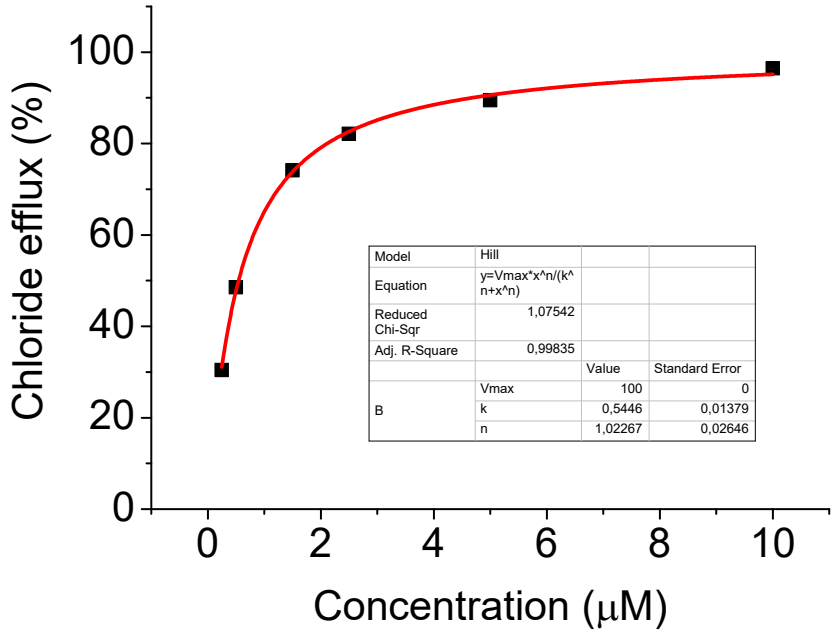


Figure S76. Hill analysis for compound **L8**.

Cl^-/HCO_3^- exchange assays

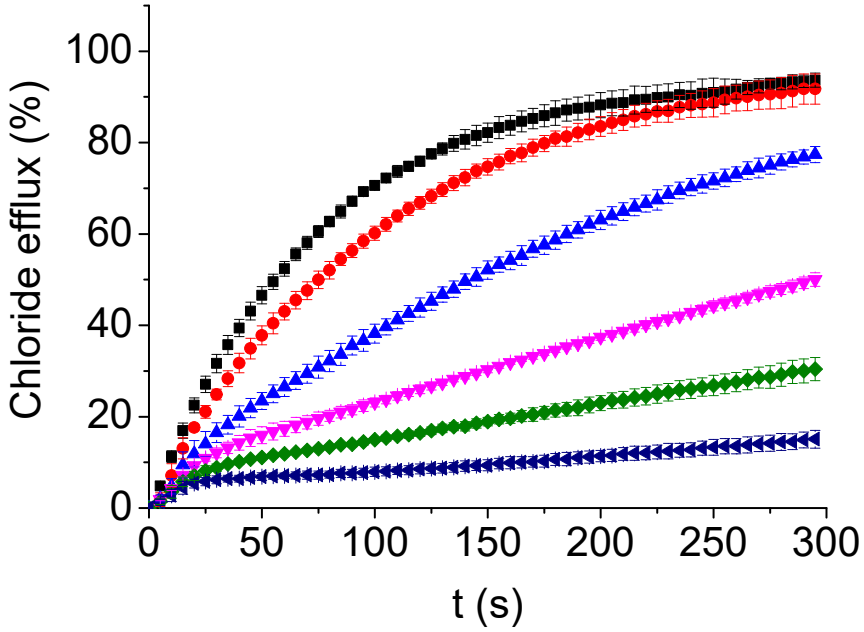


Figure S77. Chloride efflux promoted by compound **L1** (25 μM, black; 15 μM, red; 5 μM, light blue; 1.5 μM, pink; 0.5 μM, green; 0.25 μM, dark blue) in unilamellar POPC vesicles. Vesicles, loaded with a NaCl solution (451 mM NaCl and 20 mM NaH_2PO_4, pH 7.2), were immersed in a Na_2SO_4/$NaHCO_3$ solution (150 mM Na_2SO_4, 40 mM $NaHCO_3$ and 20 mM NaH_2PO_4, pH 7.2). Each trace represents the average of at least three trials, performed with three batches of vesicles.

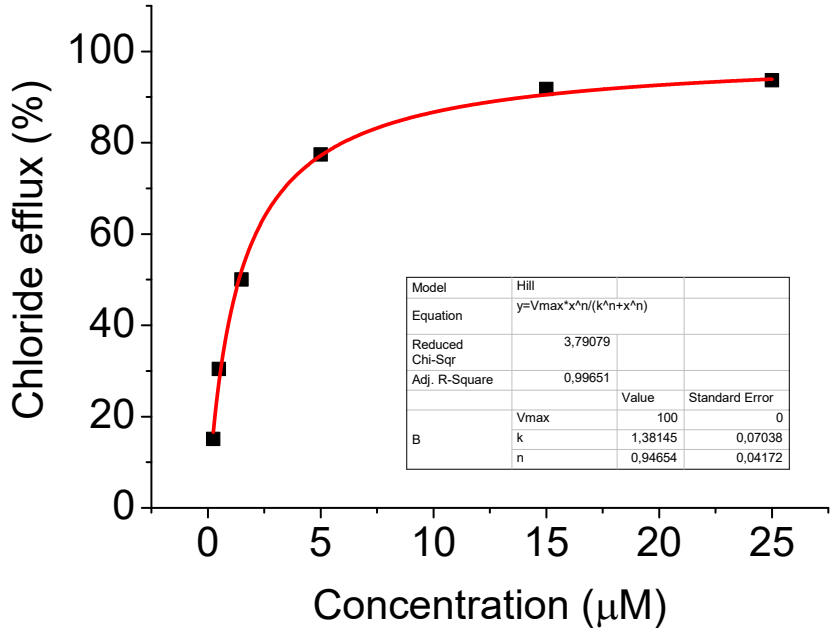


Figure S78. Hill analysis for compound **L1**.

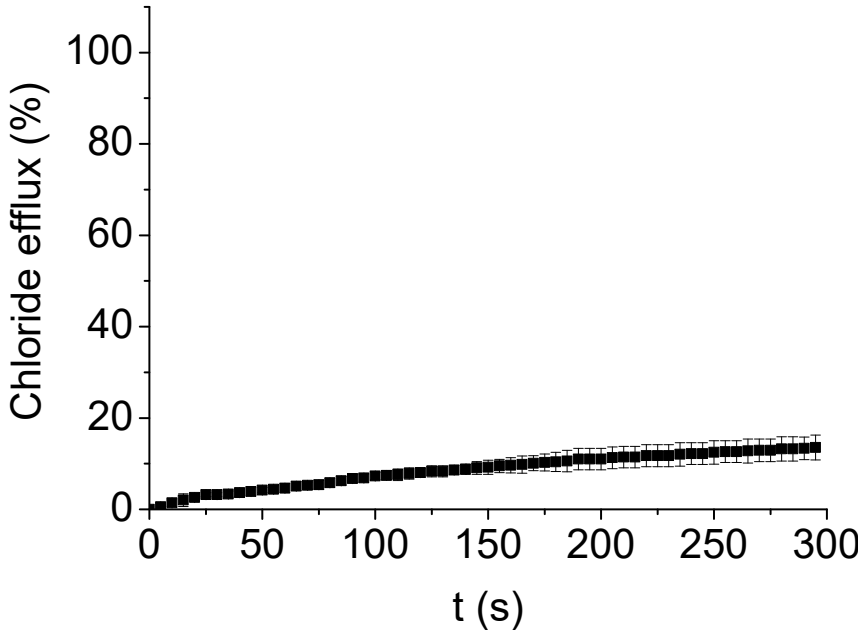


Figure S79. Chloride efflux promoted by compound **L2** (5 μM, black) in unilamellar POPC vesicles. Vesicles, loaded with a NaCl solution (451 mM NaCl and 20 mM NaH_2PO_4, pH 7.2), were immersed in a Na_2SO_4/$NaHCO_3$ solution (150 mM Na_2SO_4, 40 mM $NaHCO_3$ and 20 mM NaH_2PO_4, pH 7.2). The trace represents the average of three trials, performed with three batches of vesicles.

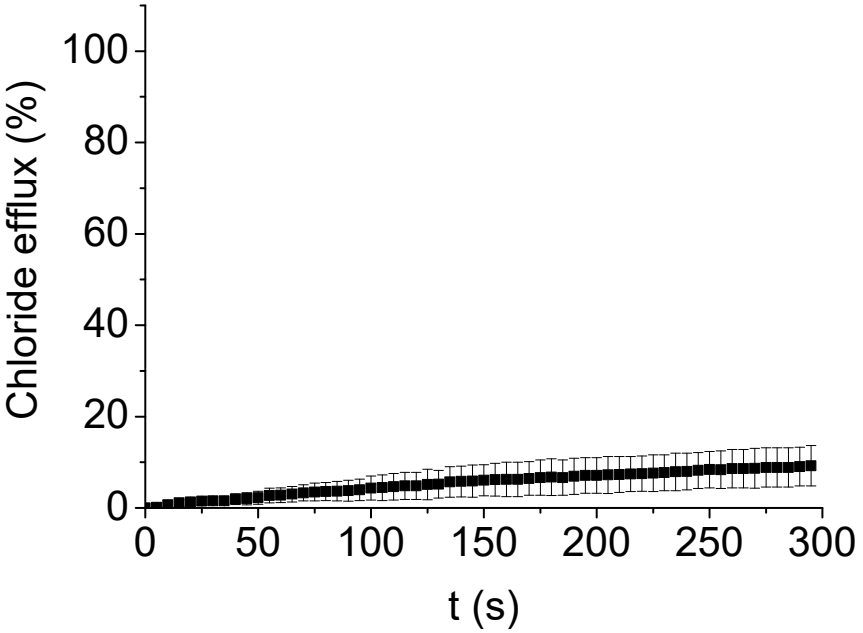


Figure S80. Chloride efflux promoted by compound **L3** (5 μM, black) in unilamellar POPC vesicles. Vesicles, loaded with a NaCl solution (451 mM NaCl and 20 mM NaH_2PO_4, pH 7.2), were immersed in a Na_2SO_4/$NaHCO_3$ solution (150 mM Na_2SO_4, 40 mM $NaHCO_3$ and 20 mM NaH_2PO_4, pH 7.2). The trace represents the average of three trials, performed with three batches of vesicles.

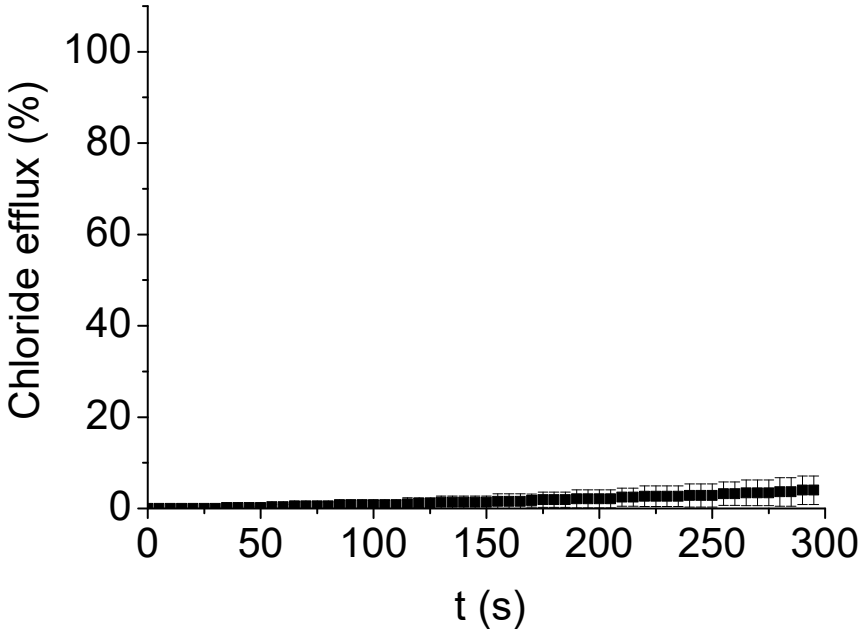


Figure S81. Chloride efflux promoted by compound **L4** (5 μM, black) in unilamellar POPC vesicles. Vesicles, loaded with a NaCl solution (451 mM NaCl and 20 mM NaH_2PO_4, pH 7.2), were immersed in a Na_2SO_4/$NaHCO_3$ solution (150 mM Na_2SO_4, 40 mM $NaHCO_3$ and 20 mM NaH_2PO_4, pH 7.2). The trace represents the average of three trials, performed with three batches of vesicles.

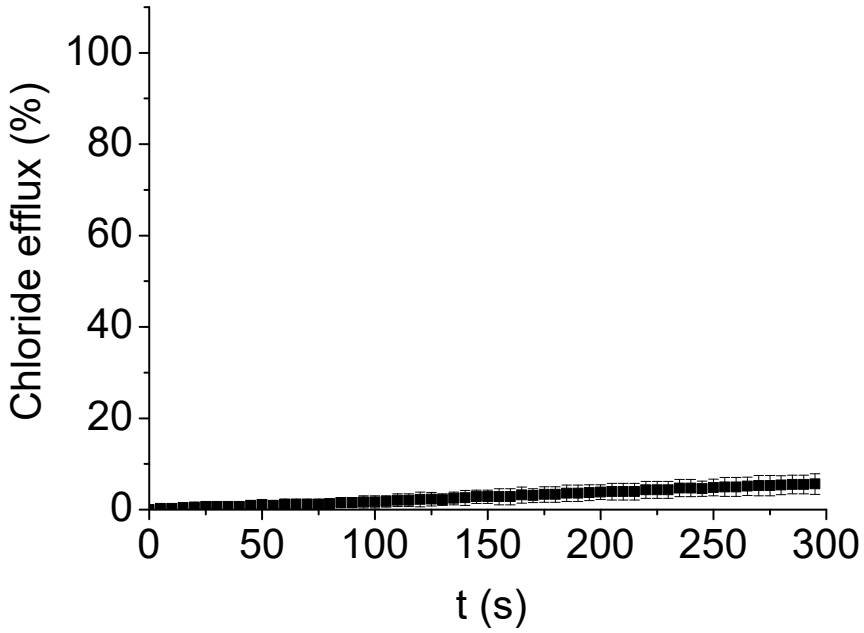


Figure S82. Chloride efflux promoted by compound **L5** (5 μM, black) in unilamellar POPC vesicles. Vesicles, loaded with a NaCl solution (451 mM NaCl and 20 mM NaH_2PO_4, pH 7.2), were immersed in a Na_2SO_4/$NaHCO_3$ solution (150 mM Na_2SO_4, 40 mM $NaHCO_3$ and 20 mM NaH_2PO_4, pH 7.2). The trace represents the average of three trials, performed with three batches of vesicles.

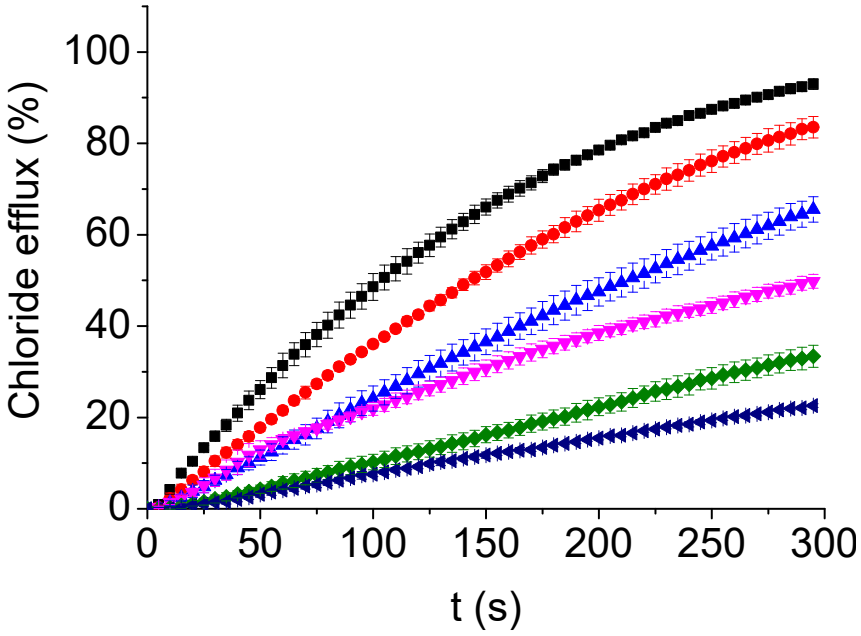


Figure S83. Chloride efflux promoted by compound **L6** (10 µM, black; 5 µM, red; 2.5 µM, light blue; 1 µM, pink; 0.5 µM, green; 0.15 µM, dark blue) in unilamellar POPC vesicles. Vesicles, loaded with a NaCl solution (451 mM NaCl and 20 mM NaH_2PO_4, pH 7.2), were immersed in a Na_2SO_4/$NaHCO_3$ solution (150 mM Na_2SO_4, 40 mM $NaHCO_3$ and 20 mM NaH_2PO_4, pH 7.2). Each trace represents the average of at least three trials, performed with three batches of vesicles.

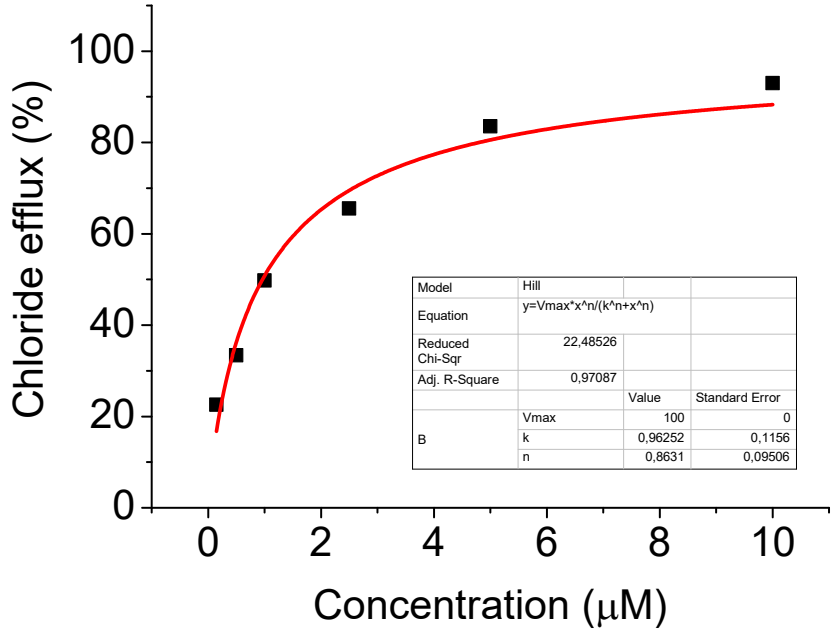


Figure S84. Hill analysis for compound **L6**.

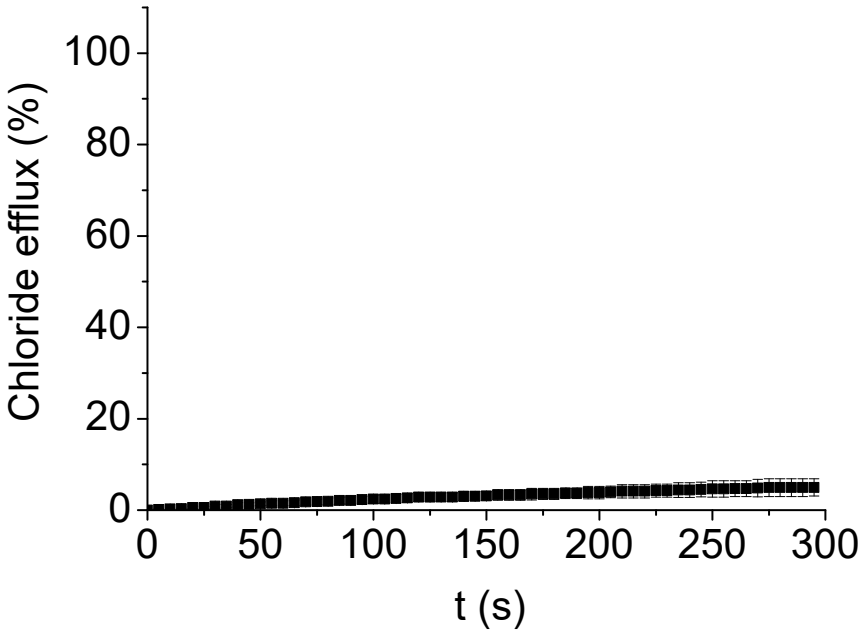


Figure S85. Chloride efflux promoted by compound **L7** (5 µM, black) in unilamellar POPC vesicles. Vesicles, loaded with a NaCl solution (451 mM NaCl and 20 mM NaH_2PO_4, pH 7.2), were immersed in a Na_2SO_4/$NaHCO_3$ solution (150 mM Na_2SO_4, 40 mM $NaHCO_3$ and 20 mM NaH_2PO_4, pH 7.2). The trace represents the average of three trials, performed with three batches of vesicles.

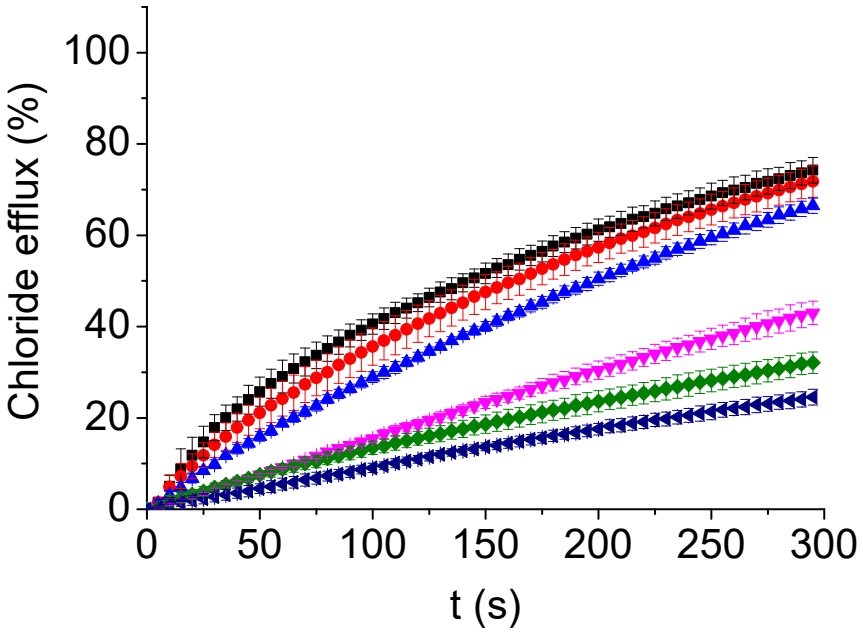


Figure S86. Chloride efflux promoted by compound **L8** (25 µM, black; 20 µM, red; 15 µM, light blue; 5 µM, pink; 2.5 µM, green; 1.5 µM, dark blue) in unilamellar POPC vesicles. Vesicles, loaded with a NaCl solution (451 mM NaCl and 20 mM NaH_2PO_4, pH 7.2), were immersed in a Na_2SO_4/$NaHCO_3$ solution (150 mM Na_2SO_4, 40 mM $NaHCO_3$ and 20 mM NaH_2PO_4, pH 7.2). Each trace represents the average of at least three trials, performed with three batches of vesicles.

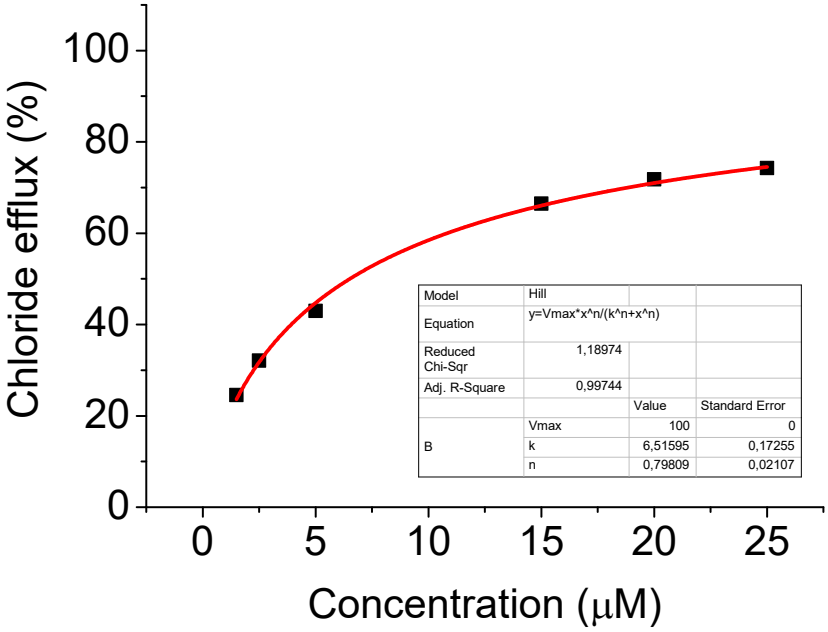


Figure S87. Hill analysis for compound **L8**.

5.3. Emission spectroscopy transport experiments

5.3.1. Carboxyfluorescein-based assays

Vesicles made of POPC were loaded with a NaCl aqueous solution (451 mM NaCl, 20 mM NaH_2PO_4, 50 mM CF, I.S. 500 mM, pH 7.2) and treated according to the procedure described in *Section 5.1*. The experiments were performed in 1-cm disposable cells, the final POPC concentration in the cuvette being 0.05 mM and the total volume 2.5 mL. At t = 60 s an aliquot of a solution of the corresponding compound in DMSO (or the blank, DMSO, 1.25 µL) was added, and emission changes were recorded for 300 s. At t = 360 s a pulse of a detergent (Triton-X, 20% dispersion in water, 20 µL) was added to lyse the vesicles and free all the entrapped CF. The obtained emission value was regarded as 100% release and used to normalise the data.

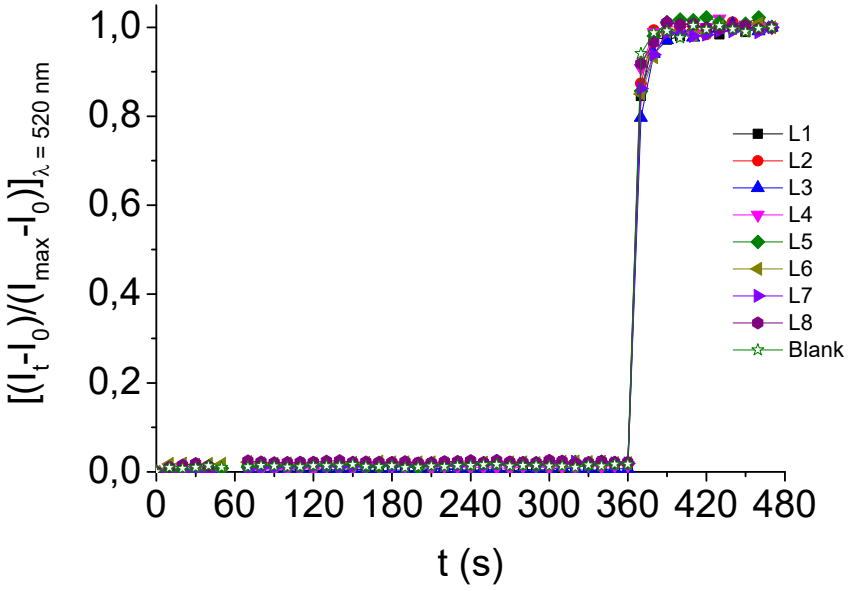


Figure S88. Carboxyfluorescein leakage observed upon addition of the studied compounds to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s the compound (0.5 µM, 1 mol% carrier to lipid concentration) was added, while at t = 360 s the detergent (20 µL) was added. The blank is DMSO (1.25 µL). Each trace represents the average of three trials, performed with three batches of vesicles.

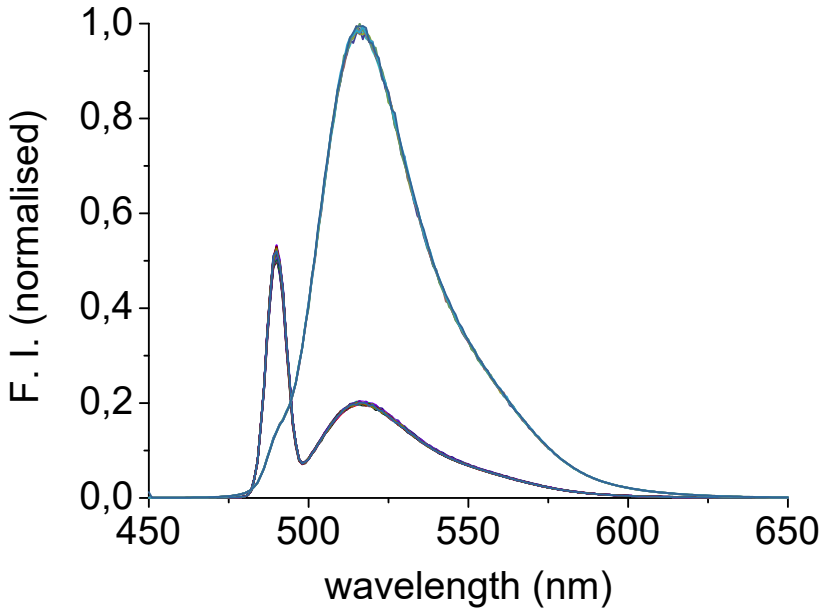


Figure S89. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of compound **L1** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s compound **L1** was added (0.5 μM, 1 mol% carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

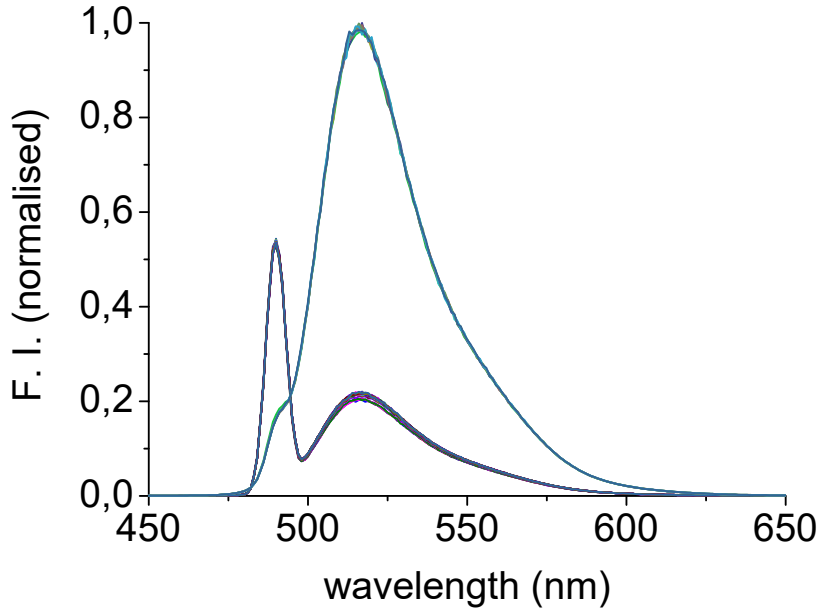


Figure S90. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of compound **L2** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s compound **L2** was added (0.5 μM, 1 mol% carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

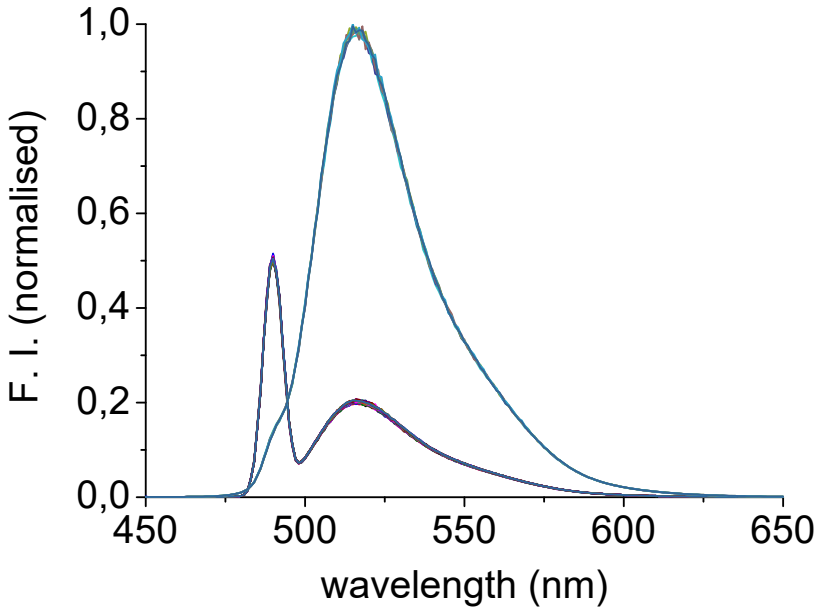


Figure S91. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of compound **L3** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s compound **L3** was added (0.5 μM, 1 mol% carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

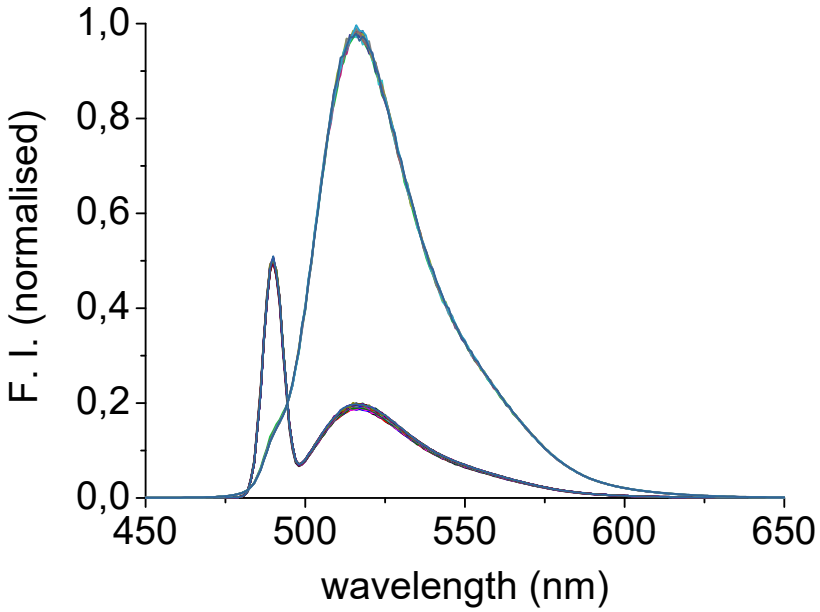


Figure S92. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of compound **L4** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s compound **L4** was added (0.5 μM, 1 mol% carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

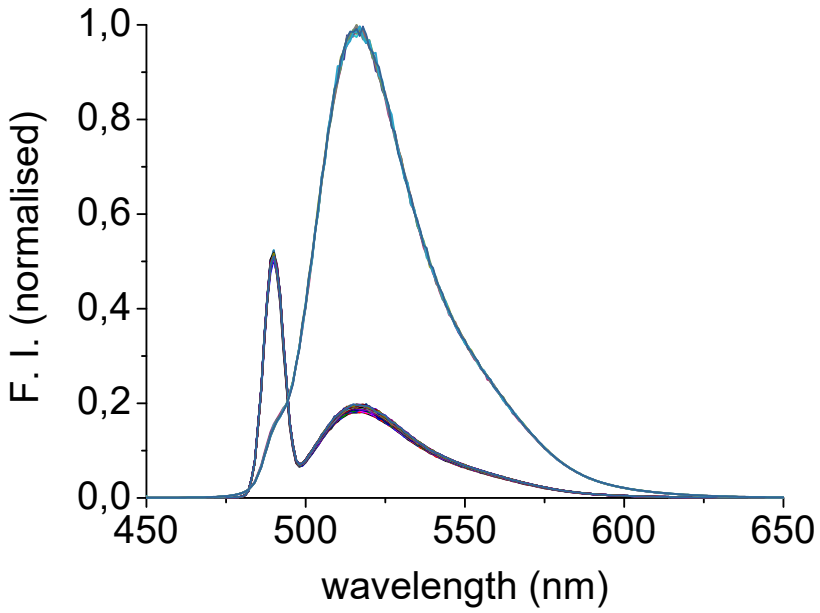


Figure S93. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of compound **L5** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s compound **L5** was added (0.5 μM, 1 mol% carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

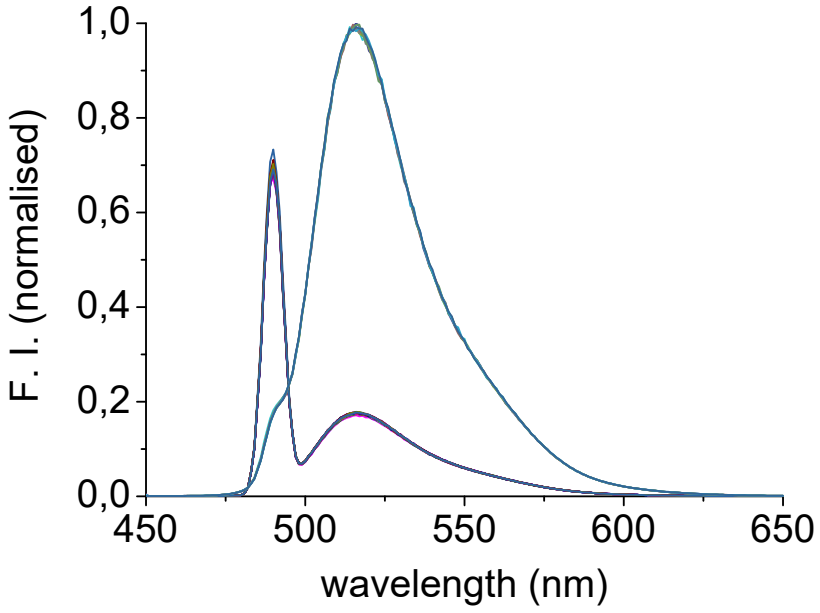


Figure S94. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of compound **L6** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s compound **L6** was added (0.5 μM, 1 mol% carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

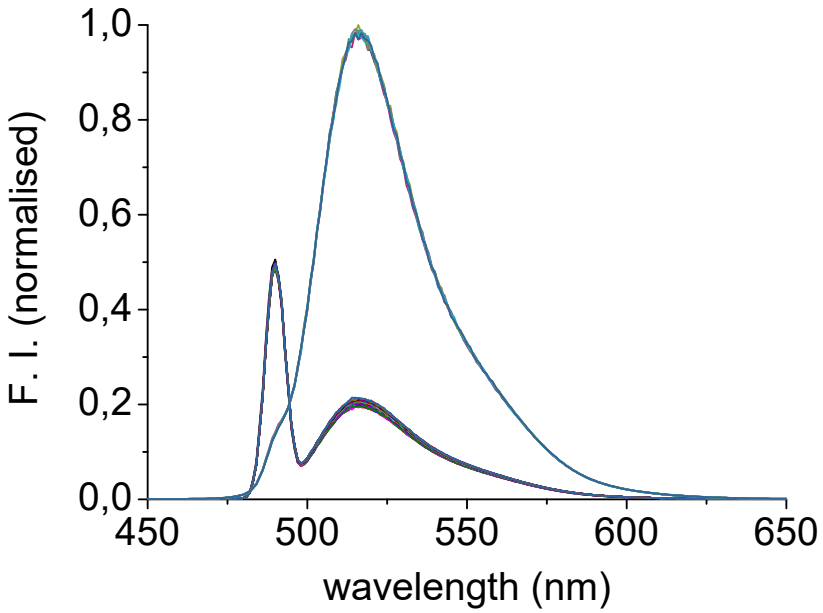


Figure S95. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of compound **L7** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s compound **L7** was added (0.5 μM, 1 mol% carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

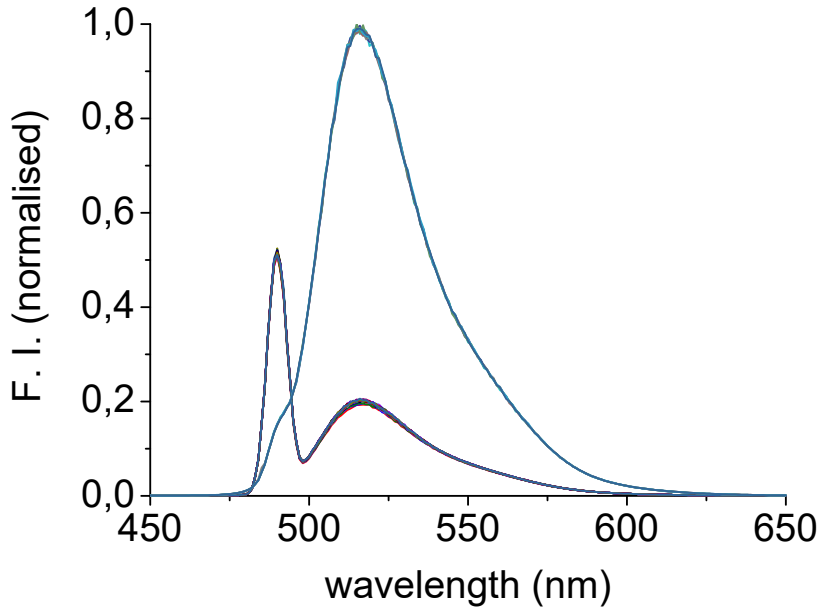


Figure S96. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of compound **L8** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s compound **L8** was added (0.5 μM, 1 mol% carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

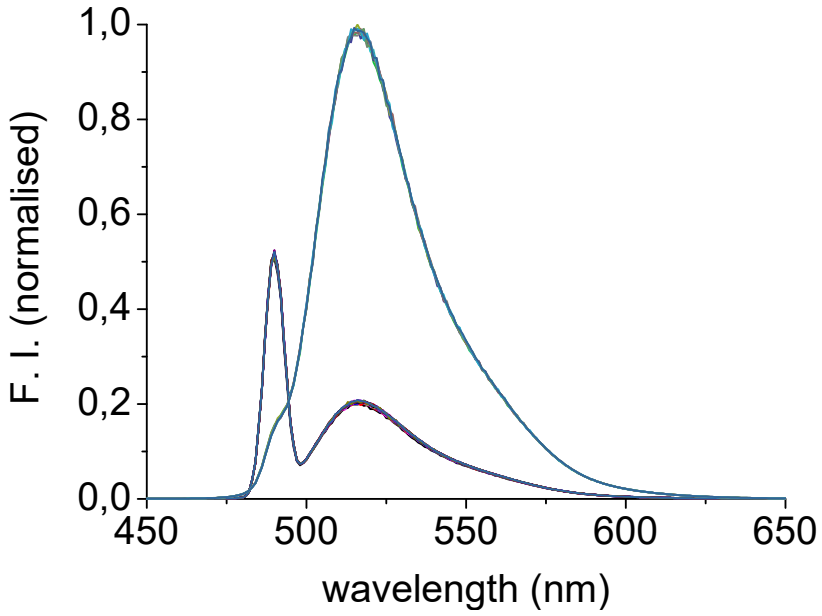


Figure S97. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of **DMSO** to POPC vesicles (0.05 mM). Vesicles (loaded with a 451 mM NaCl solution buffered at pH 7.2 with 20 mM NaH_2PO_4, and containing 50 mM CF; I.S. 500 mM) were suspended in a Na_2SO_4 solution (150 mM Na_2SO_4, buffered at pH 7.2 with 20 mM NaH_2PO_4; I.S. 500 mM). At t = 60 s **DMSO** was added (1.25 μL), while at t = 360 s the detergent (20 μL) was added. Each trace represents the average of three trials, performed with three batches of vesicles.

5.3.2. HPTS-based assays

Firstly, a calibration curve correlating I_{460}/I_{403}, the relationship between the emission intensities collected at 510 nm when exciting the sample at 460 nm and 403 nm (the excitation wavelengths of the dye's deprotonated and protonated forms, respectively) of an HPTS aqueous solution (15 nM), prepared with a $NaNO_3$ aqueous solution (126.2 mM $NaNO_3$, 10 mM NaH_2PO_4), and the pH was built. In order to do it, aliquots of a NaOH aqueous solution (0.5 M), prepared with a $NaNO_3$ aqueous solution (126.2 mM $NaNO_3$, 10 mM NaH_2PO_4), were successively added to the HPTS solution, and after each addition the ratio of emission intensities collected at 510 nm by excitation of the sample at 460 and 403 nm and the pH value of the solution were recorded. Data were fitted to an *S*-logistic model, which provided an $R^2 = 0.9999$.

7:3 POPC:cholesterol vesicles were loaded with a $NaNO_3$ aqueous solution (126.2 mM $NaNO_3$, 10 mM NaH_2PO_4, 1 mM HPTS, pH 7.2) and treated according to the procedure described in *Section 5.1*. The experiments were performed in 1-cm disposable cells, the final POPC concentration in the cuvette being 0.5 mM and the final volume 2.5 mL. At t = 30 s a pulse of a sodium hydroxide aqueous solution (12.5 μL of a 0.5 M solution) was added to obtain a final concentration of 2.5 mM of the base in the cuvette. At t = 60 s an aliquot of the corresponding compound in DMSO (or the blank, DMSO, 1.25 μL) was added, and the ratio of emission intensities collected at 510 nm by excitation of the sample at 460 and 403 nm was recorded for five more minutes. At t = 360 s a detergent (Triton-X, 20% dispersion in water, 20 μL) was added, to lyse the vesicles and balance the pH. Once stabilised, this value was regarded as the equilibrium pH (pH_{eq}).

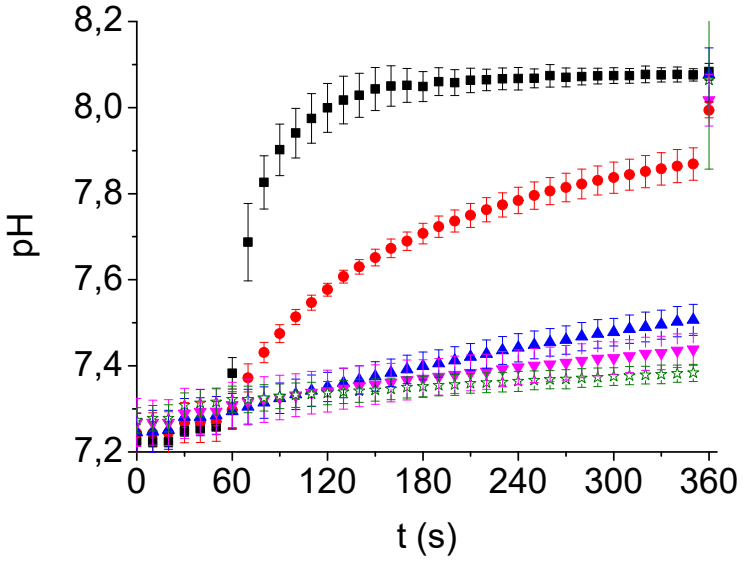


Figure S98. Variation of pH upon addition of **L1** to 7:3 POPC:cholesterol vesicles (0.5 mM POPC). Vesicles (loaded with a 126.2 mM $NaNO_3$ solution buffered at pH 7.2 with 10 mM NaH_2PO_4, and containing 1 mM HPTS; I.S. 150 mM) were suspended in a $NaNO_3$ solution (126.2 mM $NaNO_3$ buffered at pH 7.2 with 10 mM NaH_2PO_4; I.S. 150 mM). At t = 30 s an aliquot of a NaOH solution (12.5 µL, 0.5 M) was added, and at t = 60 s the anion carrier was added (0.5 µM, black; 0.05 µM, red; 0.005 µM, blue; 0.0025 µM, pink; blank, green). The blank is DMSO (1.25 µL). Each trace represents the average of at least three trials, performed with three batches of vesicles.

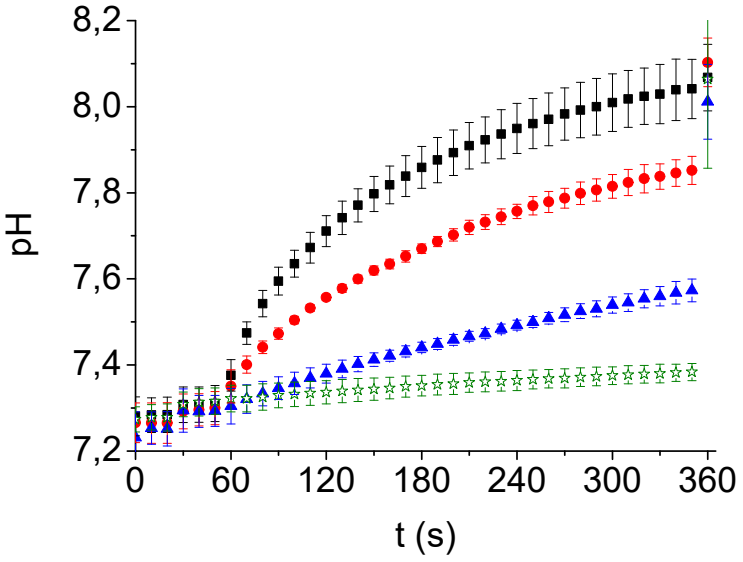


Figure S99. Variation of pH upon addition of **L2** to 7:3 POPC:cholesterol vesicles (0.5 mM POPC). Vesicles (loaded with a 126.2 mM $NaNO_3$ solution buffered at pH 7.2 with 10 mM NaH_2PO_4, and containing 1 mM HPTS; I.S. 150 mM) were suspended in a $NaNO_3$ solution (126.2 mM $NaNO_3$ buffered at pH 7.2 with 10 mM NaH_2PO_4; I.S. 150 mM). At t = 30 s an aliquot of a NaOH solution (12.5 µL, 0.5 M) was added, and at t = 60 s the anion carrier was added (5 µM, black; 2.5 µM, red; 0.5 µM, blue; blank, green). The blank is DMSO (1.25 µL). Each trace represents the average of at least three trials, performed with three batches of vesicles.

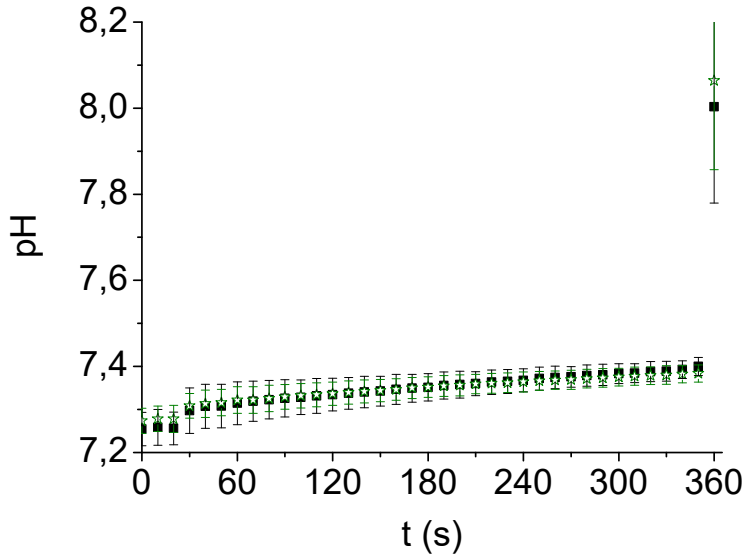


Figure S100. Variation of pH upon addition of **L3** to 7:3 POPC:cholesterol vesicles (0.5 mM POPC). Vesicles (loaded with a 126.2 mM $NaNO_3$ solution buffered at pH 7.2 with 10 mM NaH_2PO_4, and containing 1 mM HPTS; I.S. 150 mM) were suspended in a $NaNO_3$ solution (126.2 mM $NaNO_3$ buffered at pH 7.2 with 10 mM NaH_2PO_4; I.S. 150 mM). At t = 30 s an aliquot of a NaOH solution (12.5 µL, 0.5 M) was added, and at t = 60 s the anion carrier was added (0.5 µM, black; blank, green). The blank is DMSO (1.25 µL). Each trace represents the average of at least three trials, performed with three batches of vesicles.

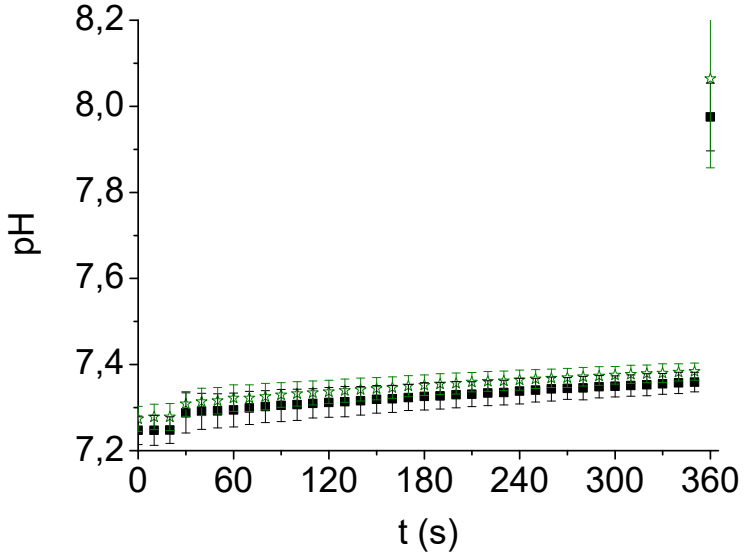


Figure S101. Variation of pH upon addition of **L4** to 7:3 POPC:cholesterol vesicles (0.5 mM POPC). Vesicles (loaded with a 126.2 mM $NaNO_3$ solution buffered at pH 7.2 with 10 mM NaH_2PO_4, and containing 1 mM HPTS; I.S. 150 mM) were suspended in a $NaNO_3$ solution (126.2 mM $NaNO_3$ buffered at pH 7.2 with 10 mM NaH_2PO_4; I.S. 150 mM). At t = 30 s an aliquot of a NaOH solution (12.5 µL, 0.5 M) was added, and at t = 60 s the anion carrier was added (0.5 µM, black; blank, green). The blank is DMSO (1.25 µL). Each trace represents the average of at least three trials, performed with three batches of vesicles.

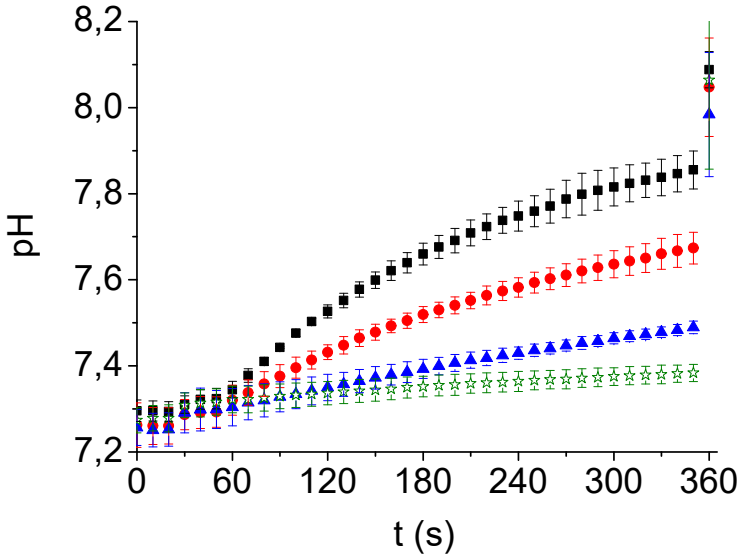


Figure S102. Variation of pH upon addition of **L5** to 7:3 POPC:cholesterol vesicles (0.5 mM POPC). Vesicles (loaded with a 126.2 mM $NaNO_3$ solution buffered at pH 7.2 with 10 mM NaH_2PO_4, and containing 1 mM HPTS; I.S. 150 mM) were suspended in a $NaNO_3$ solution (126.2 mM $NaNO_3$ buffered at pH 7.2 with 10 mM NaH_2PO_4; I.S. 150 mM). At t = 30 s an aliquot of a NaOH solution (12.5 µL, 0.5 M) was added, and at t = 60 s the anion carrier was added (5 µM, black; 2.5 µM, red; 0.5 µM, blue; blank, green). The blank is DMSO (1.25 µL). Each trace represents the average of at least three trials, performed with three batches of vesicles.

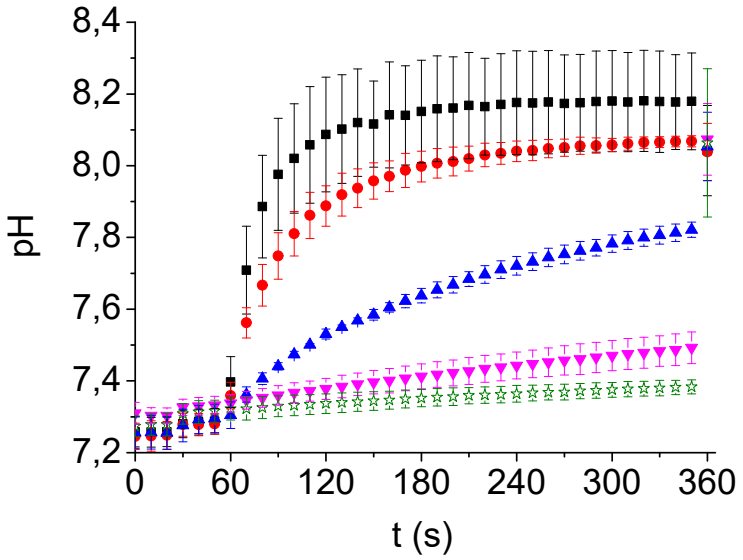


Figure S103. Variation of pH upon addition of **L6** to 7:3 POPC:cholesterol vesicles (0.5 mM POPC). Vesicles (loaded with a 126.2 mM $NaNO_3$ solution buffered at pH 7.2 with 10 mM NaH_2PO_4, and containing 1 mM HPTS; I.S. 150 mM) were suspended in a $NaNO_3$ solution (126.2 mM $NaNO_3$ buffered at pH 7.2 with 10 mM NaH_2PO_4; I.S. 150 mM). At t = 30 s an aliquot of a NaOH solution (12.5 µL, 0.5 M) was added, and at t = 60 s the anion carrier was added (0.5 µM, black; 0.05 µM, red; 0.005 µM, blue; 0.0005 µM, pink; blank, green). The blank is DMSO (1.25 µL). Each trace represents the average of at least three trials, performed with three batches of vesicles.

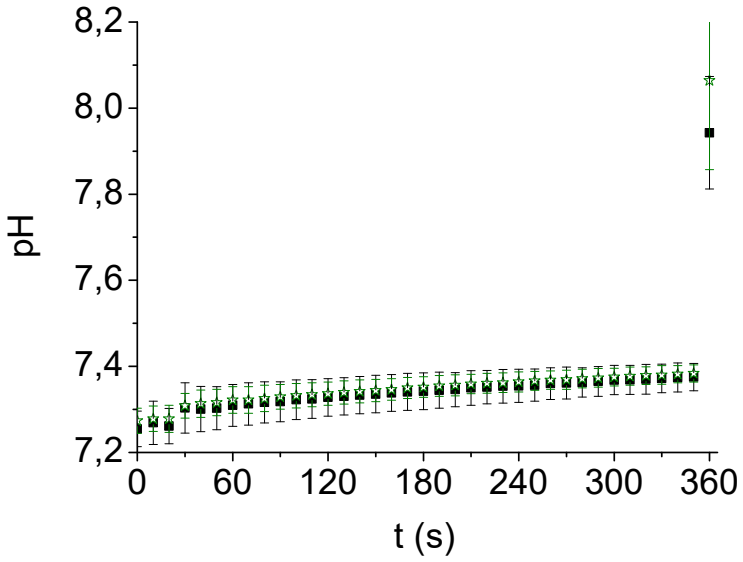


Figure S104. Variation of pH upon addition of **L7** to 7:3 POPC:cholesterol vesicles (0.5 mM POPC). Vesicles (loaded with a 126.2 mM $NaNO_3$ solution buffered at pH 7.2 with 10 mM NaH_2PO_4, and containing 1 mM HPTS; I.S. 150 mM) were suspended in a $NaNO_3$ solution (126.2 mM $NaNO_3$ buffered at pH 7.2 with 10 mM NaH_2PO_4; I.S. 150 mM). At t = 30 s an aliquot of a NaOH solution (12.5 µL, 0.5 M) was added, and at t = 60 s the anion carrier was added (0.5 µM, black; blank, green). The blank is DMSO (1.25 µL). Each trace represents the average of at least three trials, performed with three batches of vesicles.

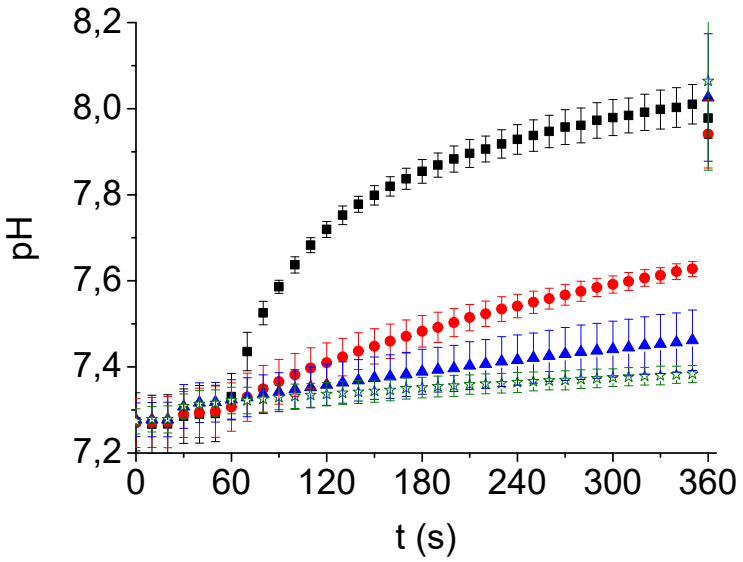


Figure S105. Variation of pH upon addition of **L8** to 7:3 POPC:cholesterol vesicles (0.5 mM POPC). Vesicles (loaded with a 126.2 mM $NaNO_3$ solution buffered at pH 7.2 with 10 mM NaH_2PO_4, and containing 1 mM HPTS; I.S. 150 mM) were suspended in a $NaNO_3$ solution (126.2 mM $NaNO_3$ buffered at pH 7.2 with 10 mM NaH_2PO_4; I.S. 150 mM). At t = 30 s an aliquot of a NaOH solution (12.5 µL, 0.5 M) was added, and at t = 60 s the anion carrier was added (0.5 µM, black; 0.05 µM, red; 0.005 µM, blue; blank, green). The blank is DMSO (1.25 µL). Each trace represents the average of at least three trials, performed with three batches of vesicles.